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Investigations concerning *Ulcus Neuroticum Mucosae Oris*.

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Stockholm.

Under different names, generally *ulcus neuroticum oris* or *ulcus aphthosum chronicum*, we find in the medical literature some notices of a disease, which is said to be very rare and the etiology of which is not satisfactorily known. In the "Dermatologische Zeitschrift" 1911 I have described two cases of this disease, up till then unknown in Sweden. Of late I have had the opportunity of meeting the same patients again and of observing also some analogous cases. These facts show, that the malady may perhaps not be so rare as we have been inclined to believe, and must therefore be regarded to be of practical consequence, all the more as it in several cases has been quite a serious illness, defying all treatment and for years causing the patients pain and discomfort.

The disease has in most cases been difficult to determine, probably on account of its being noticed so very seldom, and because it can easily at a hasty examination be mistaken for several other sickly processes, which the mucous membrane of the mouth is subjected to. At a closer study the cases in question appear, however, to have several qualities on common, which fact, as it seems to me, quite authorizes the creation of the idea of a special disease.

The attention seems to have first been drawn to the disease in America and in England through notices by Jacobi, Sibley, Kirk and Court and only later on,

especially thanks to Löblowitz, does it seem to have been introduced into German literature. I shall not here enter upon a lengthy history, but after a relation of my own cases I shall try to give, in tabular form, a summary of the accounts of the disease, which I have been able to find in the medical literature. On this basis the clinic and the pathology of the disease will afterwards be discussed.

Cases Observed by the Present Writer.

My own cases are chiefly members of two families. In one of these there are 8, in the other 2 persons, who have been suffering from the disease in question. Of these 10 cases I have had the opportunity of examining 7. Besides I have observed another case, nr 8, and thanks to the obligingness of Dr Marcus been able to observe for some time one more patient. The last mentioned case has been described by Marcus in the Proceedings of the Congress of the Northern Society of Dermatology 1913, and I shall later on give an abstract of it. With the exception of these cases, there are not, as far as I know, any other noticed and described in Scandinavia.

The family nature of the disease is best shown by means of a genealogical tree. The names of the persons, who have shown symptom of the disease, are printed in italics.

Family I.

1. G. P. farmer, married to		2. <i>Charlotte A.</i>	
3. <i>Edla P.</i> married to W—g,		4. <i>Maria P.</i> unmarried,	
shoemaker,		5. <i>Joel G.</i> married to Ada G.	
		11. son.	
6. <i>Ester</i> and 7. a twin sister			
8. <i>Ragnar</i> and 9. <i>Lily</i> (twins)			
10. son, born in 1912.			

According to reports, there have never been observed in the family any cases of tuberculosis, nervous debility, struma or abnormalities of skeleton or skin with their adnexes.

G. P. who was a farmer, appears to have been a strong and healthy man. He died more than 25 years ago of an acute illness of a nature unknown to the survivors. His wife, Charlotte P., seems to have introduced the affection of the mucous membrane into the family. She was a foundling child and it has been impossible to obtain any information as to her parents. According to the statement of her children she was nervous and of a hasty temper and had violent fits of anger even at trifling causes. From her 15:th year she suffered from recurrent attacks of sores in her mouth. She died in 1915 of a disease unknown to her family. As to the other now living members of the family, I have had the opportunity of examining all, with the exception only of Maria P. and her 9 years old son. Maria P., the twin sister of Edla W., is said to have had attacks of wounds in her mouth since her 14:th or 15:th year. Her son, who is put out to nurse in the country, is also said to have of late begun to show symptoms of the family disease, otherwise he is said to be strong and big for his age.

Case I. Joel G., aged 29, shoemaker.

As a child he has been well and of the infectious diseases he has, as far as he knows, had measles only. He denies luetic infection. Since his 15:th year he has suffered from recurrent wounds in his mouth. The symptoms growing worse with each year, he was at last, in 1911, obliged to seek medical aid in a hospital. While he was staying at St. Göran's Hospital he was examined very carefully and I shall quote the following from my article in the *Dermatologische Zeitschrift*, which has already been mentioned.

Status 3. III 1911. The patient is strongly built with well developed muscles and of normal weight. He does not convey the impression of being nervous. The inner organs are normal. No adenitis. No struma. Composition of blood normal. No skin diseases. Wasserman's test negative. Temp. afebrile. Pulse 70—80.

Lips somewhat thick, but not pathologically, teeth well preserved. On the mucous membrane of mouth there appear several subaceous glands. No foetor ex ore.

On the right tonsil and stretching across the front wall of pa-

latum molle a wound, 4—5 cm. long, 2—3 cm. wide, and in the centre about 0.5 cm. deep. On its bottom yellowish gray pseudomembrane which only with difficulty can be loosened. The borders of the wound are polycyclical, sharp, red, somewhat wallshaped and infiltrated.

Just above the second molar of the upper left jaw, there was found on the gingiva a similar more superficial sore, 0.5 by 0.5 cm. large and on the buccal mucous membrane, just behind the left corner of the mouth another sore, 1.5 by 1.5 cm. in size.

On the left border of the tongue, a few cm. from the tip, a wound as large as a hemp-seed, reddish infiltrated with a necrosis, the size of a pin's head, in the centre.

At the angle of the left lower jaw an insensitive gland, as big as a bean.

In scrapings from the wounds there were found neither bacilli fusiformae nor spirillae, only solitary cocci.

The patient complains of terrible pain in the wounds, suffers from extreme salivation and can eat solid as well as fluid food only with the greatest difficulty.

The treatment was commenced with diverse mouthwashes, radium on the wound at the left corner of the mouth, lapis causticus etc.

16. III. The wound on the left bucca which was treated with radium has grown and now reaches the corner of the mouth, it measures 2 by 2 cm. and is, besides, of the same appearance as before. The sore on the palate is unchanged, the one on the tongue has grown, and is now 0.5 by 0.5 cm. in size. On the back of the uvula, which in its entirety is somewhat swollen and red, there is now an infiltration of the size of a hemp-seed, and yellowish gray in the middle. Subjectively the patient feels somewhat better, the salivation and the difficulties of swallowing have lessened.

23. III. The wound on the left bucca considerable, the one on the palate has diminished, the one on the tongue has grown.

24. III. On the border of the anterior left palate an infiltration about the size of a hemp-seed with yellow necrosis.

26. III. The infiltration on the left palate has grown into a wound as large as a pea and of the same appearance as the others.

1. IV. The sore on the left side of the pharynx is smaller than before, here and there in its bottom there are islands of red granulations.

10. IV. At a laryngoscopic examination (Dr Arnoldson) there was found in the posterior right part of hypopharynx a wound about 2—3 cm. in size, similar to those in the pharynx and in the mouth.

15. IV. The wound on the uvula has grown, so that almost half of the latter has been eaten away. Another, about 1 by 1 cm. large wound on the left bucca. The wound on the left palate has healed, the one on the right side of pharynx has begun to cicatrize backwards and downwards, but has grown towards palatum durum.

The patient has afterwards been removed to the oto-laryngological department of Sabbatsberg's Hospital, where I had the opportunity of examining him on April 4. His state was now much worse. Besides several new wounds in the mouth and pharynx, he had a big one too on the epiglottis. The difficulties of swallowing were pronounced. He had also some reumatoid symptoms in his wrists and ankle-joints. For 2—3 weeks he had a sore on the scrotum, about 1 by 1 cm. in size and somewhat painful, in appearance similar to those in the mouth.

He grew better by and by and left the Hospital some weeks later.

16. XI. 1916. The patient called on me again. He had on the whole grown better during the last years. He had, however, rather often new attacks of wounds, but these were as a rule rather small. He had never been so ill as in 1911. His temper seemed to have grown worse, however, he is often gloomy and downcast, and has more than once thought of suicide. He also told me that he was often cold and frozen and that his mouth and pharynx grew worse as soon as he was cold or when he drank something cool. Reumatoid pains had evidently not occurred.

At the examination nothing abnormal as to the skin or internal organs was observed.

Examination of the blood (Dr. Lindbom.)

Haemoglobin, Sahli	110	
Red corpuscles	5,240,000	
White "	9,200	
Neutrophiles	59	%
Eosinophiles	2	"
Mastcells	0.5	"
Lymphocytes	32	"
Monocytes	6.5	"

On the mucous membrane of the mouth there is, on the inside of the upper lip, a wound as big as a hemp seed, of the usual appearance, and another, somewhat larger, at the frenulum linguae.

14. X. 1917. The patient relates that he has had some severe attacks of the disease in the summer. Since last week he has had terrible pains in his throat. At a laryngoscopic examina-

tion there was stated the existence of an ulcer about the size of a pea on the right border of the epiglottis.

The patient is married since 1914. No children. His wife has not had any wounds in her mouth.

After 1911 the patient has tried different kinds of treatments, internally and externally. Various gargles, solutions of nitrate of silver, iodine alcohol, Pfannenstil's treatment, radium, etc.

Internally, we have tried among other things: arsenic, quinine, bromine, KJ, Hg., salicylic preparations, thyreoidea tablets, atropine, etc. All has been in vain. Painting the wounds with tinctura gallae seems to have helped for the pain more than anything else.

Case II. Edla W., aged 41, married to a workman.

The patient has as a rule been strong and well, as a child she had measles. Wounds in the mouth now and then since she was 15 years old. During the last years, however, not so bad as before.

Status 22. III. 1911. The patient looks strong and healthy and gives no impression of nervousness. No goitre. The inner organs quite normal.

On the inside of the upper lip an infiltration, the size of a pea (said to be 2—3 days old), with a necrotic centre. The mucous membrane of the mouth and pharynx otherwise sound. Bad teeth. No adenitis.

27. III. The wound has grown larger, 1 by 1.5 cm. in size, but is only skin-deep.

15. IV. The wound has healed, cicatrization.

In June 1917. I met this patient again and has watched her for some time afterwards. Except this disease of the mouth she has been well. She now and then suffers from strong salivation and wounds. The latter, however, appear only seldom, 3 or 4 times a year, and only one or two at a time. On June 12. she showed such a wound, of the size of a hemp-seed, on the gingiva of the lower jaw.

The patient is married and has, as is seen from the genealogical tree, 5 children (2 pairs of twins), one of which is dead. All the children now alive, except the youngest one, suffer from the same disease as the mother. The husband is reported to be free from it.

Case III. Ester W., born in 1917. A twin. (The twin sister died 9 months old).

The girl has been ailing since early babyhood. She has at times, since she was 3 or 4 years old, had wounds in her mouth.

Status 12. VI. 1917. A thin, pale and, as it seems, badly nourished girl. Teeth bad, rachitic. Heart, lungs and urine are normal.

On the inside of the left bucca a reddish, tender infiltration, as large as a pin's head. On the gingiva below the front teeth an infiltration about the size of a pea, with yellow necrosis in the centre. No adenitis. No foetor ex ore. Increased salivation and pain in the mouth.

No scars visible on the mucous membrane.

Case IV. Ragnar W., born in 1909. A twin.

He has on the whole been healthy. Now and then wounds in the mouth since he was 2—3 years old. He has had only little trouble from them.

Status 26. VI. 1917. A pale, thin boy. Teeth bad, inner organs normal.

On the right frontal palate an infiltration, about the size of a hemp-seed, red and sore, with necrosis in the centre. No adenitis or foetor. Salivation not much increased.

Case V. Lily W., born in 1909, the twin sister of case IV. Has now and then had wounds in the month, like the brother.

Status 12. VI. 1917. General conditions as in case IV.

No wounds visible in mouth. On the gingiva below the left corner tooth of the lower jaw a small scar, as reported after a newly healed wound.

The next two cases are sister and brother. They belong to a family that seems strong and on the whole without any known cases of tuberculosis or any mental diseases. The father died from an accident in 1896, the mother is alive and well. Since her youth, she suffers, however, from strange pains in her mouth. Her tongue is said to feel swollen and dry and now and then to be the seat of a burning and severe ache. But it is stated that wounds have never been found there. Of the 4 children, a man, aged 33 and a woman aged 24 are well, a man aged 28 (*Case VI*) and a woman aged 21 (*Case VII*) suffer from the same disease.

Case VI. Erik J., born in 1899, debt-collector.

As a child he had measles and varicelle. At eight, he had scarlatina and in connection with this illness an affection

of the kidneys. He is reported to have had albumen in the urine for some years after, but later on he has shown no signs of it. He has had a bronchial catarrh several times and has been operated for throat abscess 4 times, last time in 1912. He has further suffered periodically from catarrh in the nose, sometimes, to judge from the description, accompanied by an inflammation of the sinus frontalis.

As a child and youth he suffered from enuresis nocturna et diurna, and he has still sometimes urinary strains, and difficulties in holding the urine. Evacuation has during the last years been slow, often with an interval of 2—3 days. He has also been suffering from gases and a feeling of congestion. He easily flushes and perspires much especially when he gets excited or anxious. Sleep and appetite have generally been good.

Since 1914 he has suffered from periodically reappearing wounds in the mouth. The symptoms seem to have been rather serious and to have shown themselves in connection with indigestion. In 1916 he sought help for his affection at the Serafimer Hospital, where he was nursed $16\frac{1}{5}$ — $23\frac{1}{5}$. From the notes made about him there, I only cite that, after a minute examination he was found to be quite well with the exception of subjective pains and wounds in the mouth. The diagnosis was stomatitis mycotica. No fungus or other mikroorganism seems to have been shown.

Status 20. VIII. 1917. A normally built man of middle height. Light, thin growth of beard. Eyes glossy, lips large, swollen, increased salivation. Skin feels cold and damp. Dermographismus. All the posterior molars are missing. In the upper jaw the two middle incisors are missing and replaced by artificial teeth. No goitre. Genitalia normally developed.

The patient is gloomy and downcast and declares that he is tired of life. He is shy of people, while he feels that his surrounding regards him as having an infectious disease. He suffers from increased salivation and pains in his mouth.

Heart and lungs are quite normal. Urine contains no albumen or reducing substance. Abdomen not tender on palpation. The examination of the gastric juice made at the Serafimer Hospital in 1916 did not show any obvious signs of illness. The total acidity, however, was somewhat high, 58. No signs of lues. Wassermann's test negative. Blood normal (Dr Lindbom).

Haemoglobin according to Sahli	100
Red corpuscles	5,180,000
White "	6,350

Neutrophiles	63 %
Eosinophiles	3 "
Mastcells	1 "
Lymphocytes	30 "
Monocytes	3 "

On the mucous membrane of the mouth there was observed at the frenulum linguae an infiltration, the size of a pea, with yellow necrosis on the surface. A similar infiltration on the right side of the palate. Tonsils normal. No foetor, no adenit.

Treatment: Tabl. thyreoid 0, 10 3 times a day.

13. IX. The patient feels worse and is more nervous than before. The before mentioned infiltrations are healing, but a new one is seen on the inside of the upper lip. Tabl. thyreoid put out. Atropine $\frac{1}{6}$ mg twice a day.

25. IX. Salivation diminished, also pains. Another wound is seen on left bucca.

25. X. The patient feels much better, he has at present no infiltrations or wounds. He does not feel so "heavy" as before, blushes less and says that he has had daily evacuation for the last weeks.

Case VII. Märta J., shop-girl, 21 years old, unmarried.

A sister of Case VI. At the age of 5 she had morbilli, varicelle and scarlatina. She had no sequelae from these diseases, and has on the whole been well and strong during the period of growth. 5 years ago she fell ill with a catarrh of the bladder and had to stay at a hospital for a month. Afterwards she has had some slight relapses of this illness. She has been obliged to seek medical aid a few times on account of pains in the stomach. Physicians have declared the illness to be a catarrh of the stomach and after having taken medicine for some time she has recovered.

About Christmas 1917, she got overworked and felt very tired and dejected. At the same time there appeared in her mouth some wounds similar to those that her brother used to suffer from. They were painful and increased the salivation. After some weeks they had healed spontaneously.

After this incident she has had several attacks of wounds of this kind. But the latter have never been numerous, generally only 3 or 4.

She states that she has always been hasty-tempered, as is also the case with the other members of her family. The menstrual flows have been normal, and there has not been observed any connection between the latter and the disease of the mucous membrane.

The last attack of wounds occurred about 2 weeks ago.

Status Nov. 14. A fair woman of middle height. Weight, skin and muscles normal. Teeth beautiful and well preserved, some of the molars filled. She feels strong and well. Inner organs normal. No goitre. She makes no impression of nervousness.

The mucous membrane of the mouth on the whole normal. On the inside of the underlip there is observed on the mucous membrane an infiltration, hardly the size of a pea, with an inconsiderable central necrosis, in the state of circatrizing. This is reported to be what remains of the largest wound of the last attack. No foetor, no adenitis.

Case VIII. Amelie W., born in 1848, widow.

At the age of 19, the patient married her cousin, a doctor. He died of diphtheria, 32 years old. They had several children. In 1868 a daughter was born, who died 2 years ago of tuberculosis. In 1870 a son was born, who became a sailor and died of the yellow fever aged 29. Next child, a girl born in 1871 is still alive and well. In 1874 the patient was delivered of a fully developed hydrocephalus, who died during the confinement. Neither husband nor children have shown any signe of the illness, for which the patient now seeks medical aid.

The patient has on the whole been well with the exception of some insignificant ailments. But she has had many difficulties and sorrows and between 50 and 60 years she has been obliged to work very hard. When she was young, she had a small goitre, but it has disappeared in later years. Menses, which always has been normal, disappeared at about the age of 50.

In 1908 she was tended on account of arsenic poisoning. The most pronounced symptoms were weariness, headache, loss of hair and loss of weight. Arsenic was shown in the flat but could not, in spite of examinations be found in the urine.

In 1915 she went through a cure for weight-reducing, as she had grown uncomfortably stout. From 1915 and till now she has reduced her weight with 19.3 kg.

2 years ago she began to have wounds in her mouth and these symptoms have returned periodically. She has been troubled with increased salivation. She reports that the attacks have been most difficult during the cold season and that they seem to appear when she has been low-spirited and dejected.

5 weeks ago the patient got a bronchial catarrh and her health suffered accordingly, as she had also, at the same time, family troubles. Simultaneously she got another bad attack of wounds in the mouth and on the palate.

Status 1. XI. 1917. A strong and healthy old lady. Weight 71 kg. She seems, however, to be rather nervous.

Heart, lungs and urine were not examined, but are reported to have been examined several times during the last years by other doctors, who have declared her to be uncommonly well for her age.

The patient's teeth are missing (since 15—20 years ago). Salivation somewhat increased. In the centre of the mucous membrane of the underlip a somewhat elongated infiltration of the size of a big pea, with yellowish gray pseudomembrane. On the front part of the hard palate the mucous membrane is somewhat infiltrated on a spot as big as a thumb's nail and covered with a yellowish gray necrotic membrane, difficult to loosen. The border of the latter is brightly red and polycyclic. No foeter, no adenitis. The pain in the mouth not at present so severe as before.

Case IX. This patient was demonstrated by Marcus at the Northern Dermatological Congress, Stockholm 1913, and the history is found in the Nord. Med. Arkiv. It runs in short as follows.

A carpenter, aged 23. 3 weeks after an acute angina in March 1912 the symptoms in the mouth showed themselves. Several serious attacks.

2. X. 1912. Inner organs normal. General loss of strength. Temp. afebrile. Increased salivation, severe pains in the mouth and pharynx. A great number of red bordered wounds with yellow, necrotic surfaces in the mouth and on the tongue. The largest wound is 3 cm. long. Wounds on the soft palate (the uvula is eaten away), on epiglottis and in larynx.

The wounds healed by and by and on December 20. 1912 he was absolutely free from symptoms. After 3 weeks a new attack. Later on several other attacks have been observed.

Treatment with radium, organic preparates, Hg, KJ, Salvarsan etc. without any effect.

Tabular Survey of Cases Described in the Literature.

Author	Time of publication	Age of the patient, sex, etc.	Time of first occurrence of the disease	Notes
Jacobi.....	1894	2 men, 1 woman	—	Nervous individuals, 2 of them insane. One man had neither beard, pubeshair nor axillarhair. Could only with difficulty keep himself warm. According to Kirk a cretin.
Sibley.....	1899	3 women. 1) Aged 74, married. 2) Aged 50, unmarried.	At the age of 50. In earliest childhood.	1) Good health in general, no insanity in the family. 10 children, no miscarriages. Symptoms of mouth sometimes very troublesome. 2) Nervous person with dyspepsy, headache and several attacks of "Hysteromania" (climacterical). In connection with outbreaks of wounds in the mouth sometimes conjunctivitis and surface wounds on the outer genitalia.
Kirk.....	1899	3) Aged 64, a widow. A woman aged 50.	3 years ago. At last menses.	Has had a very hard and laborious life, 13 children. Profuse menses. Author regards the patient as suffering from "Symptoms of thyreoidal disease before the development of general myxoedema".
Court.....	1899	A woman aged 36, married.	10 years ago.	General condition of health good. 5 children. Troubles and many sorrows.

Author.	Time of publication	Age of the patient, sex, etc.	Time of first occurrence of the disease.	Notes
Löblowitz	1910	10 persons (men and women, not stated how many of each sex.) Typical family occurrence. 1 father with 6 children and 1 mother (sister of the above mentioned man) with 2 daughters.	Early childhood.	Inner organs seem to be normal. General nervous symptoms have been especially noted for some persons. A girl suffered from neurasthenia with fits of depression lasting sometimes for months (Melancholy). All the women have had difficult menses, menorrhagias and dysmenorrhæ. They have also suffered more from the disease than the men. 1 of the cases mentioned has not been examined by Löblowitz. The above mentioned father of the 6 daughters had no wounds for 10 years i. e. since he was 40 years, and the illness had therefore never been verified by Löblowitz.
Frese	1911	2 women, 1 man. 1) aged 40, married. 2) aged 19, unmarried. 3) aged 40.	1) At the age of 15. 2) At the age of 11 or 12 years. 3) 1 year ago.	Frese evidently does not know of similar cases described before. The 3 cases observed lived in the same village and of the 700 inhabitants 2 more are said to have had the same disease. A closer relationship between the patients is not indicated.
Miculicz...	1912	3 women about 20 to 30 years old.	—	Short notice in the manual by Mikulicz and Kümmel. Patients are reported to be anaemic, respectively chlorotic.

As seen from the above, I have found in the literature 7 communications concerning observations of this disease, including in all 24 cases. With the exception of these papers there exist also some other publications by Flatau, Mandelstamm, Landgraf, Schourp, Miculicz, Freund a. o. regarding cases with similar symptoms. The statements in these communications do not allow, however, of any opinion as to the disease having been identical with the one in question.

The histories of illness collected in the table are in most cases very shortly told by the respective authors, and much desirable information is not given. Most authors have only had the opportunity of seeing solitary cases. Löblowitz alone has had a relatively rich materiel at his disposal but the latter is, however, one-sided, belonging to one family only. The addition of my own cases to the above mentioned observations concerning this singular and before uninvestigated illness has seemed to me to be so valuable, that I have not been able to abstain from bringing up the disease for discussion again.

Clinical Observations.

Symptoms of the mucous membrane. The disease can evidently appear anywhere on the mucous membrane, in the cavity of the mouth, in the fauces, pharynx and larynx. Sibley has also in one case, a female, found conjunctivitis and wounds on the genitalia in connection with attacks of the illness. In my first case there has once been observed a wound of uncertain nature on the scrotum. If the wound in any way has been connected with the disease of the mouth of the patient I cannot judge of. Similar symptoms have not appeared at recurring attacks of the affection of the mucous membrane.

The disease begins as a red granulation, similar to a pin's head, on the mucous membrane. After 1—2 days the infiltration has grown into the size of a hemp-seed or a pea and in the middle there is seen a yellowish white necrosis which only with difficulty can be loosened.

The whole develops into a grayish yellow wound, with red borders and sharp stripes. The larger wounds are surrounded by a sharp red infiltrated zone of reaction. The small wounds are round or elongated, the bigger ones sometimes have a polycyclical border.

The size of the wounds varies between a pin's head to 3—5 cm. in diameter. The same may be said of their depth. In my first case the largest wound was about $\frac{1}{2}$ cm. deep. The wounds heal spontaneously, the small ones more quickly, the larger ones more slowly. The largest wound in my first case lasted more than 2 months. The wounds heal but leave a scar, the latter also vanishes by and by.

It is typical of the illness that it occurs in fits and appears over and over again. In the easy cases there are seen 1—2 small, superficial wounds and the attacks occur 2—3 times a year, the patients being free from any ailment for months. In the serious cases with numerous big wounds one attack is hardly over before a new one sets in. The patient is almost never free from wounds.

Subjective symptoms. These depend very much on the intensity of the attack. The primary infiltrations are often by the patient regarded as an insignificant granulation on the mucous membrane, when they are first felt by the tongue. As soon as there is a necrosis a burning pain is experienced. Especially the wounds on the tongue and in the larynx appear to be painful. The pain is often said to be so terrible, that it can hardly, as it seems to me, be explained only by the small visible changes of the mucous membrane. The salivation is increased and at the severe attacks there are formed masses of glassy slime. The pains can be almost impossible to stand, and are an obstacle to the taking of any food, solid or fluid. They are increased with every movement of the lips and tongue.

General conditions. As a rule the attacks are not accompanied by any rise of temperature to speak of, neither by

adenitis or foetor ex ore. But these symptoms may of course occur at a secondary infection.

Organic changes in heart, lungs, kidneys and canal of digestion do not seem to have played any important part in the cases observed. Changes in the skin of characteristic appearances are not mentioned either. The blood was normal in the cases where it was examined i. e. in my 1:st and 6:th cases and in the case of Marcus. Mikulicz mentions quite incidentally that his patients have been anaemic, resp. chlorotic.

Of more interest is the information regarding the psyche and the nervous temperament of the patients which in several cases is found at the study of this disease.

Jacobi's cases are reported to have been "insane" types. In one patient there existed evidently endocrine disturbances, eventually idiocy. Kirk in one case considers that he has to do with a beginning myxoedem. One of Sibley's patients suffered from hysteromania as well as from several general nervous symptoms. One of Löblowitz' patients suffered from melancholy. Nervous headache, dyspepsia, dysmenorrhé, a hasty and violent temper, neurastenic tendencies are symptoms that are mentioned now and then. With my most seriously affected patients, cases I and VI, several general nervous disturbances of this kind have been observed. Both of them have been very neurasthenical and at times had suicidal ideas. In case I there has with the years developed a subjective feeling of cold and when touched, the skin, especially on the hands, felt chilly. Case VI has in childhood shown a decided enuresis nocturna et diurna. Even when he was grown-up his bladder innervation does not seem to have worked quite normally. The patient is made nervous by blushing too easily. Objectively there is stated a dermatogrfismus. He perspires much, especially when nervous. The intestinal symptoms of the patient appear to have been of a nervous nature, at least to judge from the happy effect of atropine. This fact as well as the symptom just mentioned indicate vagotoni. In several cases and this seems to have been the

fact in those examined by me, e. g. case VIII, the mouth symptoms grew worse through outer influences which had a depressing effect on the mood of the patient.

Sensibility of the skin and reflexes have been examined in my cases, but have not shown anything especially abnormal.

Time of first appearance of the disease. The sex of the patients. Heredity, etc. The disease can evidently appear at different ages. The first symptoms have in several cases been visible between 4—5 years, in others on the contrary (Sibley) not before 50—60 years, and in my 7:th case not until the age of 67. Occasionally the symptoms are said to be most painful from 15—30 years (Löblowitz), and to lose in intensity later on. This is not always the case, however. Sibley for instance relates that one of his patients at the age of 74 had painful attacks.

Men as well as women are smitten with the disease. Up til now, however, it has been more frequently found among women. Of the 36 cases known by me, 8 have been men and 18 women. Besides, there are the 10 cases of Löblowitz, where there is no statement as regards sex, (that 5 at least were women, is quite evident though).

Löblowitz found the most troublesome attacks with his female patients. Among my own cases, however, the most hardly smitten were men (cases I, VII).

The disease seems often to have been a family feature, as in the cases examined by Löblowitz, Frese and the present writer. Among the cases of Frese 2 were mother and daughter. The third case followed by him and a fourth one of which he had heard occurred in the same village. If these last cases have been related to one another or with the first ones is not reported. In my cases there is no sign of consanguinity. As to this, nothing is known about the other histories of illness. In the first family described in this paper there is a strong disposition for twin births. In the same family we also see that the

disease has begun, in the first generations at about 14 or 15 years, in the later generations much earlier, at the age of 4—5 years. In the second family described here, the disposition for the disease has not been so strong, as only two of its members have suffered from it. But it is very remarkable that the mother sometimes has suffered from a scorching feeling and smarting pains in the tongue. It almost seems as if we had here a more harmless form of the disease without infiltration and wounds.

*Histological examinations*¹ from excidated efflorescences have been made by Frese, Marcus and the present author. The results agree, and only show the picture of an ordinary inflammation without any characteristic features at all: a loss of epitel and in its place a fibrous pseudomembrane, roundcell infiltration in the mucosa and down into the submucosa.

These examinations are made on excidated pieces of efflorescences, which have already been subject to necrosis or ulceration. Earlier states, i. e. primal efflorescences before the formation of necrosis, and later states of healing should be examined in order to make the anatomic picture more clear. That I have not made these completing investigations depends on the fact that in the only case which I have had the opportunity of attending to at a hospital, the wound after the primary excidation was very painful and long in healing. The patient has afterwards decidedly refused to allow any fuller clinical experiments.

With patients, treated ambulatorily, it is difficult to watch the relatively short, first state, as the patients do not seek any assistance before the formation of necrosis, when the subjective symptoms have appeared.

Any communication of the results of a post-mortem examination does not exist, as far as I know. As is seen from the above, none of my own patients have died.

¹ cfr the supplement, page 130.

Bacteriological examinations have been made in some cases. Frese has examined scraps from the necrotic patients as well as excised parts of the wounds. He could only show solitary staphylococci.

Löblowitz reports that he has only found solitary microorganisms and these have probably been of secondary origin. He found varying staphylococci, short, thick and long, somewhat bent staffs, as well as large refringens-like spirochaetae. In some, as he says, secondarily infected, stinking wounds with foul coatings, there were found in pure culture the fusiform bacilli and spirochaetae typical for angina Vincenti.

Marcus has in vain sought for diphteria bacilli and for bacillus fusiformis.

In all my cases scraps from the wounds have been examined, according to the Indian ink method of Burri and after direct dyeing with carbol fucsin or Füger's methylen blue. The results have on the whole agreed with those described by Löblowitz: solitary cocci or refringens-like spirochaetae. In the small fresh wounds the bacteriae flora has been much more scanty than in the older ones. In my cases Nr I and VI (as in Frese's case) attempts at cultivation have been made on diverse substrates with no other result than a growth of staphylococci and streptococci. Cases I, II and VI have been tested for diphteria. The result was negative. In sections from cases I and VI no tuberculosis bacilli could be shown. Inoculation on the skin of the stomach of scraps from the wounds gave negative results in case I.

Syphilis has not been found in any case and Wassermann's reaction has in the cases where it has been tried (Frese's woman of 19, Marcus' case and my cases Ns. I, II and VI) been negative.

Differential Diagnosis.

At the diagnosis of this disease, the anamnesis is very important, as one of the most characteristic traits of the illness is its fitful appearance, as well as the capacity of spontaneous healing of the efflorescences. But at a differential diagnosis one must, however, reckon with almost all diseases that cause ulcerations on the mucous membrane of the mouth and pharynx.

The disease which we must first consider is *stomatitis aphthosa*. This illness is however, as a rule much quicker in its course, and has less subjective difficulties. The whole process is there much more superficial and causes only an erosion of the epithelium cover. But here the disease begins as an infiltration, which gets a necrosis in the centre, forms a real ulcer and heals with the formation of a scar.

The diseases belonging to the *herpes* group begin with the formation of bladders, which is never the case here. In connection with herpes efflorescences on lips and skin are often found. The herpes bladders on the mucous membrane are often of short duration, that is true, but they leave, however, traces in the shape of fringes of epithelium around a superficial ulceration of the mucous membrane. There is never any formation of bladders here. The wounds are deeper and are surrounded by a sharp wall of infiltrations.

What has been said of the herpes group is on the whole true also of the *pemphigus* group, though the solitary efflorescences there are larger and the symptoms generally more malignant.

Erythema multiforme is sometimes located to the mucous membranes and is inclined to recurrences. The most common place on the mucous membrane is on the lips. There also generally appear efflorescences on the skin. As a rule there are no yellowish white necroses, but the seats of disease — most often bladders — get a more cyanotic, bluish

red appearance. The attacks are generally followed by a rise of temperature.

There does not seem to be any reason for discussing *cancer* and *tuberculosis* in this connection, as it is the question of a disease that occurs in attacks and passes spontaneously.

As to *syphilis*, the superficial sores may perhaps resemble secondary papulæ, the deep wounds gummata. By means of the usual methods of examination, spirochaetae examination, Wassermann, potassium iodine ex Juvantibus etc., a mistake can surely easily be avoided.

Leukæmia can sometimes cause gangrenous and ulcerous processes in the mouth, nose and pharynx. A complete examination also of the state of the blood must therefore not be neglected in dubious cases.

Angina Vincenti is the disease which perhaps has to be most seriously considered at a differential diagnosis. The absence of foetor ex ore, adenitis, fever and above all of typical microorganisms must be taken into account here. But it should also be remembered that in certain cases (e. g. Löblowitz) the neurotic sores get infected and a real angina Vincenti can thus develop. But this is nevertheless a secondary phenomenon, a relatively rare complication, as it seems.

Besides the illnesses now mentioned, there are several others, which may show singular symptoms in the mouth, as *epidermolysis bullosa hereditaria*, *foot and mouth disease* (*stomatitis epidemica*), *sporothricosis*, *blastomycosis*, etc. The danger of confusion with these diseases cannot be so great that we need discuss it here.

Pathogeny.

As to the causes of the disease there have been different opinions. It is above all two theories which have been discussed, namely 1) the theory of the disease being infectious and depending on a specific organism and 2) the theory of the nervous origin of the disease.

It is only natural that the possibility of a contagious affection has been thought of. Most authors, however, have denied this hypothesis. The strange course of the illness, the absence of fever, adenitis and foetor ex ore as well as the ineffectiveness of all therapeutic attempts with locally applied antiseptica are in a certain way against it. The only one who has nevertheless defended this view is Frese. He admits, though, that the foundations for this theory are very uncertain. In spite of careful bacteriological examinations, he has not been able to find other bacteria than solitary staphylococci. Also from other quarters the bacteriological examinations have on the whole given negative results. It seems above all to have been the observation that several cases have occurred in the same village, and of these 2 in the same family, that has caused Frese to stand up for the possibility of an infectious disease. But it must be remembered, that he has not known of earlier statements of similar histories of illness and the conditions present there, which in a certain degree have denied the theory of the infectious nature of the disease.

If we scrutinize more carefully the conditions of the cases of disease occurring in the same family, we find just here, as it seems to me, a rather strong evidence against the supposed contagious nature of the illness, which should according to this view be caused only through some specific virus. It appears, e. g. from the genealogical tree shown by the present writer, that the individuals that have married a sick person (man or woman), remain untouched by the disease. Their children, however, are often strongly disposed for it.

Mikulicz and Kummel point out, that the disease is rather like a typical tropical disease, *aphtae tropicae*, also called Indian spruw, cronical tropical diarrhoea, etc. The patients suffering from this affection show as a rule, except pains in the mouth, also a high degree of anaemia. The cause of the symptoms is then connected with a severe chronical enteritis. If the sores in the mouth here

are regarded as caused directly by some kind of virus or depend perhaps on the nervous system, is not known by the present writer. Mikulicz says himself, that in his cases of chronically recurrent aphthe, the possibility of the presence of any tropical illness is excluded, as none of his patients had ever been in the tropics. This is probably true of most cases of this sickness that we know of, at least it holds good of those observed by me.

The assumption of a neurogenical origin of the disease has won more approbation. Jacobi, who first described the affection, regarded it as a trophoneurotic symptom in psychally deficient individuals. This view has later on been taken by Sibley. Any closer explanation of the mechanism of this trophoneurosis was not given.

Kirk points out, that the sickness most probably is a thyreogene symptom. He builds on the observation that in one of Jacobi's cases as well as in his own, secondary thyreogene changes have existed according to his view and further on, on the well-known fact that changes in the mucous membrane of the mouth, e. g. swollen, fissured tongue, are not rare in connection with myxoedem. The endemical character of the illness in e. g. Frese's case, would surely if it had been known by Kirk, been another proof of this hypothesis. I for my part do not believe that it in all cases is possible to regard the disease as an endocrine disturbance. At a later examination of the patients described, it has not, with the exception of the statement concerning case VIII, that the patient when young had a slight goitre, been possible to detect any sure signs of changes in the inner secretions. The thyreoidea treatment has in vain been tried by me in cases V and VI, and by Marcus in his case.

Löblowitz explains the disease as an angioneurosis as defined by Kreibich, i. e. a disease comparable to e. g. herpes simplex, urticaria and prurigo. This explanation seems rather acceptable.

According to Kreibich the angioneurotic changes of the skin depend on an increased sensibility in the vaso-

dilatoric centra. This sensibility can arise through organic (e. g. inflammatoric processes) or functional diseases in the nervous system (e. g. hysteria) or at autointoxication (e. g. at disfunction of endocrine glands). The causes may thus be of different nature, but the result as a whole is the same.

It is evident that we are here on the plane of hypotheses and as yet unproved speculations. The angioneurosis theory of Kreibich has also been subject to much discussion and critic and he has thus won antagonists as well as followers. He may be right or wrong, it is however a fact that his view of the so-called angioneurotic dermatoses is a very good working hypothesis.

When comparing the disease described here with the neurotic gangrene of the skin, according to Kreibich a typical angioneurosis, I believe that the analogy between them must be regarded as very striking. The course of the last-mentioned disease is in short as follows: The skin on circumscribed places becomes hyperaemic, a "kvaddel" or papula is formed. After some time the latter necrotises in the centre and a crust is seen. By and by the crust is knocked off and healing with a scar follows spontaneously. The attacks which may return periodically during 10—20 years, generally cause burning and aching pain. Fever is not the rule. Any specific microorganisms have not been shown in the primal efflorescences. The multiple spontaneous skin gangrene is often called "neurotic" or "hysterical" on account of the psychic changes often shown by the patients.

Douterlepont has described a case of multiple skin gangrene, where similar changes in the mucous membrane of the mouth occurred and these sores seem to have been very like those of the illness discussed here. This case of course increases the inclination to place the neurotic skin gangrene together with the so-called chronically recurring aphte.

The fact that the subjectic symptoms of this disease often are said to be much more grave than would be ex-

pected, to judge from the changes in the mucous membrane, is more easily explained when the disease is regarded as a neurogenic affliction. The same is the case with the often made observation, that troubles and sorrows and on the whole everything that has a discouraging effect on the patient, can provoke or aggravate the symptoms.

In a few words I must also remind the reader of some other strange illnesses of the mouth, the *glossodynia* and *Möller's glossitis*, *glossodynia exfoliativa*. The subjective symptoms are there much more conspicuous than the objective ones. As a rule the patients are plainly neuropathic individuals and the diseases, which are intensely chronic, often grow worse, or better by attacks in connection with changes in the physical condition of the patient. The diseases evidently show great similarities with the one described here. It is on the whole only the changes of the mucous membrane that do not agree. Very interesting is the statement that the mother of my VI:th and VII:th cases had suffered from a disease of the mouth, which evidently was some form of glossodynia. This fact quite strongly points out that there has existed some connection between these diseases.

The Name of The Disease.

Jacobi, who considered the disease as a trophonourous gave it the name of *ulcus neuroticum mucosae*. This name has later on been kept in the English literature. Löblovitz also speaks of *ulcus aphthosum chronicum* or the chronically recurring aphtae, a name which is also found in Mikulicz. Frese has suggested the name of *stomatopharyngitis disseminata*.

For the present it seems to me to be most suitable to keep the name originally given by Jacobi, partly while it is the one most commonly used in literature, partly because this name most closely accords with the conception of the pathogenesis of the disease.

Treatment and Prognosis.

As to the treatment of the disease, it has up to now given rather depressing results. Local applications of diverse means in the shape of paints and gargles as well as different interne medications have been tried in vain. See case I.

When the pains are intense, it may sometimes be quite necessary to try paints with cocaine or some other anesthetics, especially before meals. Narcotica and sedatives are difficult to dispense with at the most severe attacks. The avoidance of exciting antiseptic gargles and hard food is quite a matter of course.

An improvement of the general state of health, when the latter leaves something to be desired, is of course quite necessary. The most important thing, however, is to improve the psychical state of the patients. A change of air, general strengthening treatment of the nerves have in some cases been helpful. A hospital stay does not seem to be necessary as a rule, and may quite certainly be altogether bad, see case I. The patients should if possible be given the impression that the disease is without danger, and by means of regular work be prevented from letting their thoughts dwell upon it.

The prognosis seems to be *quoad vitam*, good, *quoad valetudinem*, bad. It is a matter of course that the patients in the bad cases are in a distressing situation and the prospect that the painful wounds will heal spontaneously is certainly a consolation, but not a very good one, compare to the thought that a new attack generally is to be expected before long.

Supplement.

After this paper was finished, I had the opportunity of examining histologically a primal efflorescence of Case VI. The patient came to see me on December 2^d. 1917, and had then another severe attack of wounds in

the mouth. A painful granulation of the size of a hemp-seed was then excised almost at the frenulum linguae. The surface of the granulation was not ulcerated, the mucous membrane covering it was vividly red, being paler in the middle.

The piece was fixed in 5 % H. CHO, hardened in alcohol, embedded in paraffin and cut in series. Staining: haematoxylin-eosin, ironalum-haematoxylin-v. Gieson, Unna-Pappenheims staining, polychrom methylen blue.

The most characteristic change is an oedem in the papillar body. The fibrillae of the intercellular substance are broken, lymphatic vessels, interspaces and veins are distended. The walls of the vessels are hyperplastic. Small accumulations of connective tissue cells and solitary plasma-cells are found not only along the vessels but also immediately under rete Malpighii. In the epithelium is also observed a hydrops. This is most clearly shown in the stratum spinosum. In some places the epithelium cells are broken, forming a necrosis in the stratum spinosum. Below these parts there is as a rule seen a more considerable accumulation of the elements of connective tissue in the stratum papillare.

No microorganisms have been found.

The changes, in the first place oedem and dilatation of vessels, are very similar to those occurring in cases of urticaria. It is impossible to draw any positive conclusion from the microscopic examination. But the theory of an angioneurosis seems, however, to have gained a certain support from the histological picture.

The course of an efflorescence seems in short to be as follows. Primal vasomotoric changes with oedem in the stratum papillare. Later on an oedem and necrosis in the epithelium (and eventually also necrosis in the stratum papillare). Reactive accumulation of the corium cells, especially around the necrosis. Secondarily there may be other inflammatoric symptoms, e. g. roundcellinfiltration etc. on account of infection through the common bacterias of the mouth.

Further histological examinations are of course desirable in order to strengthen the weight of the observations made here and render the picture complete.

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¹ I have not been able to obtain the original work of Jacobi, and so have only read it in abstracts from different quarters.