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Pemphigus

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INDEX

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALEDNAR OF EVENTS

Visitors Welcome
February 23 - February 28, 1948

No. 191

Monday, February 23 -- HOLIDAY

Tuesday, February 24

8:30 - 10:20 Surgery Reading Conference; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.

9:00 - 9:50 Roentgenology Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans' Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; E. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. L. Visscher; Eustis Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; Leo G. Rigler and Staff of University Hospitals; M-515, U. H.

Wednesday, February 25

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Tyyrotoxicosis; Carcinoma of the Sigmoid Colon with Perforation; E. T. Bell, O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Infectious Disease Rounds; Todd Amphitheater, General Hospital, Veterans' Hospital.

Thursday, February 26

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-515, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans' Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

12:00 - 12:50 Physiological Chemistry Seminar; Observations on the Chemical Cytology of Normal Blood and Hemopoietic Tissues; Fern Anderson; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

4:00 - 4:50 Bacteriology Seminar; Subject to be announced; John Ordal; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Thoracic Surgery Conference; Richard Varco; Eustis Amphitheater.

Friday, February 27

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Treatment of Acoustic Neuromas; William T. Peyton and Kent Olson; New Powell Hall Amphitheater.

12:00 - 1:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Class Room.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, February 28

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U. H.

8:00 - 9:30 Psychiatry and Neurology Grand Rounds; Staff; University Hospitals.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M515, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; M-515, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 12:20 Anatomy Seminar; Action potentials of the cat's motor cortex with antidromic stimulation; Martin A. Adson; Localization in the ventral horn of the spinal cord; George Dingman; 226 I. A.

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NOTICE

In referring patients to dentistry, please send them directly to the Hospital Dental Clinic and not to the Dental School. This is for the purpose of having the hospital card at hand when the oral examination is made as well as for other reasons.

H. B. Clark, D.D.S.

II. PEMPHIGUS

Isadore Fisher

The term pemphigus dates back to the very beginning of medicine. Hippocrates made reference to pemphigoid fever, an acute febrile condition accompanied by cutaneous vesiculation. Febris pemphigodes was a term used by Galen in his description of what was probably Herpes Labialis. Pemphigus as a distinct entity probably was not recognized by the ancients, but apparently was looked upon as a severe manifestation of a number of bullous diseases.

No description of a disease resembling pemphigus is to be found in the literature of Medieval Europe. There is some question as to whether the first well recognized case was described by Von Grafenberg in 1596 or Koenig in 1681. De Sauvages observed, accurately described, and included his first case in a classification of cutaneous disease in 1725. Later men like MacBride and Wichman included it in their texts. In 1808 Robert Willan, the Father of Modern English Dermatology distinguished the two forms: acute and chronic Pemphigus Vulgaris.

A recognition of special forms soon followed. Cazenave classified pemphigus foliaceus as a special type. Neumann in 1886 first described Pemphigus Vegetans.

In 1919 Thost referred to another form--chronic benign pemphigus of the mucous membranes. Senear and Usher in 1926 reported 11 cases of a group to which their names have become attached. Kaposi described a chronic crusting low grade form of pemphigus which was similar or identical with the now called Senear-Usher type.

A classification of pemphigus now includes the following forms:

Pemphigus Vulgaris, the common form, is manifested by bullae of various types scattered over the body. The mucous membranes, face, neck, trunk and extremities may all be involved at one time or another. The bullae with their various, serosanguinous or hemorrhagic centers may rupture to form crusted erosions or may involute without rupture.

Brocq divided Pemphigus Vulgaris into two forms, one which was the acute form which ran a short course and had an extremely high mortality rate and the other was the chronic form with which we are more familiar. Lever found the mortality rate in the acute group to be 94% with an average duration of 9 months. Sixty seven per cent of this group were Hebrews. A common observation has been that in this form, a high percentage of the patients are Jewish. In 55% of Lever's cases the buccal mucosa was the site of the first lesion and at some time during the disease oral lesions occurred in 85% of the patients. These painful denuded areas make eating almost impossible and contribute to the rapid decline of the patient. The average age of onset in Lever's group was 52.

The chronic and more common form of Pemphigus Vulgaris runs a slower course with many patients living for several years. Lever reports the onset at the average age of 61. Oral lesions appeared in about 49% and the mortality rate was 31%. This statement is tempered with the knowledge that patients with Pemphigus Vulgaris may have remissions lasting for several years. Rare forms of involvement of the urinary bladder with Pemphigus lesions have been reported.

Luczynski stated that most primary lesions appeared in the mouth as blisters, blebs or ulcerative stomatitis. Numerous authors feel however that the primary lesion may occur almost anywhere on the body and frequently develop following trauma.

Pemphigus foliaceus is a rare form of the disease which may begin as Pemphigus Vulgaris. The early bullous lesions that develop on normal skin, soon rupture, forming yellow crusts which are attached centrally and are free at the margins. Frequently the blebs form incompletely, collapse and new bullae develop beneath them so rapidly as to give the scaling and crusted appearance of a universal exfoliating dermatitis. It was in this condition that Nikolsky described his sign as a diagnostic differential feature between Pemphigus

Foliaceus and Pemphigus Vulgaris. The Nikolsky test is based on the poor adhesive quality of epidermal layer. On slightest pressure the bulla may be moved along without rupture or he worked along leaving a collapsed larger bleb which includes the original area. The test is not pathognomonic but is sometimes seen in other bullous diseases such as Ery thema Multiforme and Dermatitis Herpetiformis as well as the various forms of Pemphigus. Pemphigus Foliaceus spreads rapidly and when it is universally distributed over the body the patient may have the appearance of one with Exfoliative Dermatitis. Because of the lamellated crusting there is much more decomposition of the skin resulting in a disagreeable odor. The hair may be lost. Lever cited a mortality rate of 56% and felt that the disease could be extremely chronic. In checking the literature he was unable to find a description of oral lesions in a true case of Pemphigus Foliaceus. Complete recovery has been reported in a number of patients with Pemphigus Foliaceus disease.

A Brazilian endemic form of Pemphigus Foliaceus has been described by Vierra. It is believed to be contagious and quite separate from the usual form of Foliaceus Pemphigus. It is a disease seen at all ages, more common in females and manifested by dystrophy of the nails, alopecia, localized elephantiasis and keratotic lesions as well as exfoliation. Vierra divided the disease into the acute, subacute, superacute and chronic forms. The subjective symptoms of pain and burning has earned this disease the name of Fogo Salvagem or The Wild Fire.

Pemphigus Vegetans appears first as a bullous eruption but the bullae soon rupture and their base becomes the origin for vegetating grouped plaques but retain their individual characteristics. They too give rise to a disagreeable odor. In women the groin is a common site for the lesions and gives the appearance of verrucae acuminata. The disease may first appear as a condylomatous perianal pigmented masses. The grouped lesions may occur on the trunk and extremities as well but do not tend to become universal. The disease with its remissions and exacerbations may last for years.

The Senear-Usher Syndrome has been designated "Pemphigus Erythematodes" by Ormsby. The two distinct features that distinguish this form are first, an eruption over the butterfly area of the face, and "V" of the neck and shoulders which resembles chronic Lupus Erythematosus and second, facial involvement resembling seborrheic dermatitis. The Lupus Erythematosus like lesions are discoid and possess a lightly attached crust. On the body large or small bullae usually develop giving way to large denuded areas. The seborrheia-like picture may be seen on the trunk also as manifested by thick greasy scales and crusts. Frequently the dry form is seen two or more years before bullae develop. Oral lesions are rarely seen in Pemphigus Erythematodes. Most cases eventually become a true Pemphigus Vulgaris or continue as an indefinite Senear-Usher syndrome. The patient does not go on to develop Lupus Erythematosus instead of Pemphigus.

The most innocuous form of Pemphigus is localized and referred to by the titles "Ocular Pemphigus" or "Benign Pemphigus of the Mucous Membranes". Klauder in his excellent review considered this a chronic benign disease that had a predilection for mucous membranes and always produced scarring in contrast to the other forms of pemphigus which rarely scar. It is slowly progressive generally occurring late in life. The patients general health is not affected. Besides the conjunctival involvement, mucosal lesions may be seen in the mouth, throat, nasopharynx, vagina and on the prepuce. The eye involvement appears more commonly at the inner canthus leading to scarring, shrinkage of the conjunctiva, obliteration of the fornices, and impairment of mobility of the globe. In 1941 Cowan and English reviewed the causes of blindness in 31,352 eyes to find ocular pemphigus the causative factor in 22 cases. Eye involvement may occur as an accompaniment in Pemphigus Vulgaris also. Scarring occurs in all mucous membrane involvement of Pemphigus Conjunctivae. There have been other patients reported in which there was a limited skin involvement adjacent to the body orifices has occurred and has also been followed by scarring.

The etiology of pemphigus remains unknown. The 4 outstanding theories as to the cause revolve around the possibilities that pemphigus is due to: (1) Infection, (2) Toxic agent or agents, (3) A disturbance of internal secretion, (4) A neuropathologic state. The usual slow onset, with a primary lesion appearing sometime before the generalized eruption, suggests an analogy to other eruptive infectious diseases. More than 20 years ago the possibility of a virus agent was introduced. Landford was able to produce sickness and death in rabbits after the introduction of the contents from Pemphigus bullae intravenously, intraspinally, intracorneally, or subcutaneously. Urbach and Reiss used vesicle fluid to produce paralysis in experimental animals. Urbach and Wolfram later inoculated vesicle fluid subdurally to pr duce symptoms of an encephalomyelomeningitis in rabbits. They were successful in carrying passage through the animals using brain substance from others previously infected. They were also able to carry out complement fixation tests on patients' blood, by using vesicle fluid or brain extract from infected animals as the antigen. A number of workers have been unable to confirm these findings.

Welsh in 1934 isolated a streptococcus from positive blood cultures of patients with Pemphigus and produced death in mice with injection of blood from these patients. Cultured bullous fluid yielded the same anaerobic, pleomorphic organism. The use of this organism produced lesions in animals consistent with Pemphigus. Bullae could be produced by injecting the killed organism into the skin of patients with Pemphigus.

In 1938 Dostrovsky, et al, were able to induce encephalitis in 43% of their rabbits after the intravenous, intracerebral or intracisternal injection of vesicle contents or blood serum from Pemphigus patients. They suggested that their organism might be an accompanying virus but not the true cause of Pemphigus.

Grace and Suskind inoculated irradiated mice intracutaneously with bacteriologically sterile blister fluid to produce encephalo-myelo-meningitis. These workers felt that their organism was not identical with that described by Urbach and Wolfram.

Some interesting changes in water and salt metabolism occur in Pemphigus. These changes vary with the severity of the disease and its rate of progression. In acute Pemphigus these changes are most marked. Lever and co-workers found abnormal serum concentrations of sodium, potassium, serum proteins, and non-protein nitrogen, as well as water distribution. They felt that these changes in blood chemistry might be a method of distinguishing the acute from the chronic form of Pemphigus Vulgaris. The acute form has already been distinguished clinically by the early development of mouth lesions, a rapid fulminating course, and a high racial susceptibility as evidence by the fact that 80% of their cases were Hebrews.

The sodium concentration was less than 132 milliequivalents per liter one or more times in all patients when oral lesions were present. Three of their patients showed a sodium concentration of 120 milliequivalents per liter shortly before death. This decrease of 20 milliequivalents per liter was indicative of a profound disturbance in acid base balance. The degree of depression in sodium level was associated with the severity of the clinical condition and the area of skin involved. In many cases the serum potassium level rose as the serum sodium dropped. The highest concentration of potassium was 12.7 milliequivalents per liter. In one case the level receded to 4.9 milliequivalents per liter only to rise to 14.9 milliequivalents per liter with an exacerbation.

Abnormal concentrations of chloride was not as marked as the sodium change. The lowest chloride level reported was 85.6 milliequivalents per liter in one of their patients. The calcium level also decreased during a crisis. Post mortem examination in 2 of their patients revealed adrenal cortical damage.

On the basis of these findings, Lever and co-workers treated 5 of their cases of acute pemphigus vulgaris with adrenal

cortical extract and sodium chloride parenterally. An improvement in the clinical picture was produced. In one patient this improvement persisted only during the administration of the drug. In 2 patients, regression took place and persisted for 3 plus years at the time of the report. The authors felt that the blood changes were a secondary manifestation in pemphigus but that a correction brought about symptomatic improvement that justified the attempt. Sulzberger failed to duplicate their results in his trial on only 1 patient.

A drop in the serum protein level with a change in the albumin globulin ratio also takes place in pemphigus. This may be accounted for by the loss through bullosis fluid and the continuous oozing.

In chronic pemphigus the changes studied at Massachusetts General Hospital showed a serum sodium level below 135 milliequivalents per liter and a similar number had a change in blood chlorides. A restoration of the acid base balance did bring about clinical improvement in one of their cases of chronic pemphigus.

An increase in the plasma volume and interstitial fluid volume was also reported by this group. They compared their findings with Gilson's report of an average plasma volume of 43 cc. per kilogram of body weight and average interstitial tissue fluid of 20% of body weight. Those patients with acute pemphigus studied in remission showed plasma volumes up to 70 cc. per kilogram and 7 to 10 kilograms of excess interstitial fluid.

Kurnick, Lever and Talbott studied sodium levels in the red cell in pemphigus. An increase of cell sodium from the normal of 12 to 14.9 milliequivalents per liter up to 25.6 milliequivalents per liter occurred in 2 of their patients. The erythrocyte membrane in pemphigus, as in the normal, was found to be impermeable to potassium.

Several studies of blister fluid values have been made. Ganssler found the blister fluid level of sodium chloride to be 500-650 mg. per 100 cc. Pitts and Johnson found the sodium, potassium and calcium levels of vesicle fluid to be lower than that of serum. Lever and Talbott found that when the chloride level was elevated, the sodium level accompanied it and the potassium and N.P.N. levels were lower than that of serum. In pemphigus vulgaris acutis the concentration of sodium and chloride was lower while the content of potassium and non-protein nitrogen was higher in blister fluid than in serum. In the chronic form of pemphigus the ratio seemed to be reversed. Cornbleet felt that the differences in ionic concentrations could be explained on the basis of Donnan's equilibrium.

Numerous attempts have been made to study the histo-chemistry of pemphigus with some attempt at explaining the mode of production and possible cause of the bullae. To date none of the findings are of significance.

In line with the blood chemistry changes in pemphigus may be the findings of Pels, Macht and Ostro. In 1929 Pels and Macht described their phyto-pharmacologic method for confirming the diagnosis of pemphigus. Based on the knowledge that living matter responds with some degree of sensitivity to the action of chemicals or toxic substances applied to it, an attempt was made to test for certain toxic metabolic products elaborated in the body. Any deleterious effects on plant protoplasm would indicate the presence of abnormal blood constituents in whatever disease was being tested. Pels and Macht used the seedling of Lupinus albus in their tests because of its long straight root. Three days after planting the seedlings are of a convenient 20-30 mm. length for testing. These are then placed in upright test tubes with a mixture of nutrient physiologic solution (Shive solution) and the blood to be tested. A consistently greater reduction of growth was reported with pemphigus serum than with other blood sera used. In 1947, Macht and Ostro made the statement that this result of the test had been confirmed in 90-95% of pemphigus patients examined. These two workers tested the effects of x-rays on open glass vials of pemphigus serum in order to produce detoxification. The method worked to their satisfaction. According

to Macht and Ostro if irradiation of a specimen detoxifies it while the untested specimen gives a toxic reaction, in their opinion the diagnosis of pemphigus is firmly established. The results of the Pels-Macht test has been open to question and after 18 years is not well accepted. At the University Hospitals it has not been of any help in making a differential diagnosis.

It might be well to consider the treatment of pemphigus as it pertains partially to the toxic picture. For many years arsenic in one form or another has been used as a therapeutic agent. This metal has been administered in the form of tryparsamide, arsphenamine, sodium arsenate, iron cacodylate, carbarsone and acetarsone. At times encouraging results have been seen with the last named drug. Germanin, also called Naphuride, Bayer 205 or suramin is a urea compound that has also been used with varying success in pemphigus. More recently Lever and Talbott and others have reported some good results in the acute phase with the use of adrenal cortical extract and sodium chloride parenterally. Viosterol has also produced improvement in the hands of some dermatologists. On the basis of this fact, plus the lowered blood calcium in some patients with chronic pemphigus, Lever and Talbott tested the effect of dihydrotachysterol. The use of this drug restored the concentration of some of the chemical constituents of the blood and also lowered the blood volume in their patients. The drug was recommended as an additional therapeutic tool. Clinical improvement was noted in 9 of 10 patients treated.

Grace and Hellman reported the recovery of 2 patients with pemphigus following the administration of 500 cc. of citrated blood from recovered cases. Urbach used a single injection of serum with a questionable effect. The use of divided doses of "convalescent serum" from a quiescent case of pemphigus was attempted here. Two patients were treated with 4 injections at intervals of 3 days for a total of 100 cc. of serum. In one patient, an elderly female with pemphigus erythematodes, a questionable transitory improvement was noted. The second case was that of a 51 year old male who had been treated at the Veterans Hospital at intervals since November 1946 with indifferent results. Coincident with the administration of convalescent serum this patient's skin cleared, his general condition improved and he was allowed to go home. This case is reported for what it may be worth and not because any conclusions can be drawn from it.

Pemphigus is a disease with a variable course and varying effects. Few accurate statistical studies of this disease have been made due to the fact that only a small number of cases of this uncommon disease is seen at any one institution. Kaposi in 1896 stated that he had seen 300 patients in the wards at Vienna plus 100 private patients. He estimated that 25% of the ward patients died in the hospital and that 30-40% more died shortly after going home. Gillis and Glass made a survey of 170 patients with this disease admitted to Bellevue Hospital from 1911 to 1941. Fifty per cent of these patients died in the hospital while an additional 33 died after discharge, making an early mortality rate of 69.4%, with 48 patients unaccounted for. According to them the earliest lesion appeared in the mouth of 31% and on the trunk in 37.8%. A history of trauma just prior to onset of the disease was frequently obtained. Weight loss and anemia were found to be a prominent feature. Necropsies were obtained in 9 of their patients. In 2 cases autolysis of the adrenal with hyperemia of the medulla was recorded. In another case the adrenals were enlarged and the cortex thickened and nodular. In one case, changes characteristic of an acute glomerulonephritis were found.

An indication of the relative incidence of pemphigus can be obtained from a review of cases seen at Massachusetts General Hospital. Out of 50,427 new Dermatology patients seen from 1921-1936, there were 63 cases of pemphigus---a ratio of 1:840. In the group were 38 patients with pemphigus conjunctivae. Twenty six, or 68%, of the patients with Pemphigus Vulgaris had mucous membrane lesions first. The average interval for the development of cutaneous lesions was 16 weeks. The mortality rate in the

group was 79% with 25 patients dying within the first year. Five more died within the next 2 years. The mortality rate among those with oral lesions was 84%. Of 4 patients still alive, 1 had been free of lesions for 4 years, 2 had a moderate number of lesions and 1 was confined to bed with pemphigus. The average duration in the 4 living patients was 9 years. The average age of onset was 57 years.

Pemphigus Foliaceus was seen in a younger age group with an average onset of 38. The mortality rate was 43% with the deaths occurring within 3 years. In 5 patients who were still alive the disease had been active 22, 21, 17, 11 and 6 years with an average duration of 15 years.

No deaths occurred in the benign group of 10 patients with Pemphigus Conjunctivae. The process was bilateral in 9 of the 10. Knapp had previously reported an incidence of cutaneous lesions in 3/4 of such patients.

In 1941 Eller and Kest published their review of 77 patients with Pemphigus. Fifty-six cases were in Jews, 47% of whom were Russian born. In the entire group there were 48 females and 29 males. The youngest patient was 17 and the oldest was 78. Fifty-one per cent of their patients had oral lesions at some time during the course of the disease. Fifteen of the patients had remissions varying from a few weeks to many years. Four of these had remissions on two separate occasions. Concomitant diseases in the group were arteriosclerosis, cardio renal disease, diabetes mellitus and gall bladder disease. In 11 no significant changes were demonstrated. In one case the liver, spleen, and adrenals were enlarged.

Lever and Talbott reviewed a series in 1944. They reported 100% mortality rate in the acute form of Pemphigus Vulgaris, The average duration of which was 7½ months. The prognosis in Pemphigus Foliaceus is also grave. Fruhwald reported a mortality rate of 73%. The mortality rate in Pemphigus Vulgaris Chronicus was 50% and in the foliaceus form was 43%. In this latter form the age at onset seemed to be important an the prognosis. In the younger age group the mortality rate was considerably lower.

Other writers have reported autopsy findings in Pemphigus. Among the prominent findings are included microscopic hemorrhages in the brain, and fatty degeneration of the liver. In one case Corey found 10-12 small gray white bodies attached to the dorsal ganglia, in the thoracic and lumbar portions of the cord. Some degeneration of the cells in the dorsal root ganglia were seen, suggesting to him that pemphigus was of neurogenic origin.

The following is a review of autopsies performed at the University of Minnesota Hospitals on patients dying of pemphigus. From 1911 through 1947 there were only 27 cases out of a total of approximately 50,000 autopsies. Of the 27, 16 were males and eleven were female patients. The youngest patient was 29 and the 3 oldest were 80 years of age. In 25 of the patients the ages varied from 44 through 80. Twenty-one or 77% of the group were 50 or more years old. In 19 of the cases the disease had been present 6 months or less with 5 of these patients ill for less than 1 month. There were no Jews in the entire group. Twenty-six of the patients had Pemphigus Vulgaris and there was one case of Pemphigus Foliaceus.

Included in the long and motley group of findings at autopsy are:

1.	Fatty degeneration of liver	9
2.	Cloudy swelling of liver and kidneys	6
3.	Broncho pneumonia	8
4.	Hypostatic pneumonia	5
5.	Pulmonary infarction	5
6.	Splenitis	5
7.	Chronic passive congestion of liver	4
8.	Coronary sclerosis	3
9.	Portal cirrhosis	2
10.	Pulmonary congestion	2
11.	Brown serous atrophy of heart	2
12.	Pulmonary embolus	
13.	Coronary thrombosis	
14.	Acute bacterial endocarditis	
15.	Anaphylaxis	

Incidental findings included myoma of the stomach, papillary cystadenoma of the ovary and early syphilitic aortitis. The anaphylactic death occurred during transfusion when the patient suddenly became warm, dyspneic and died 20 minutes after the transfusion was started.

In 22 of the cases the adrenals were found to be normal. In the other 5 the reported abnormal findings were adenoma, autolysis, degenerative change, medullary softening and slight hemorrhage in the medulla. None of these may be any more than incidental findings at autopsy.

The examination of the brain in 1 case revealed no pathologic change.

An attempt was made to correlate the autopsy findings of those patients treated at the University Hospitals with their laboratory studies. Fifteen of the cases had been University Hospitals patients. In this group was one case of Pemphigus Foliaceus and one Senear-Usher Syndrome. There was no increased incidence of the disease in any national group. One patient had been born in Poland, 2 in Sweden and 2 in Norway. The remaining patients had been born in the United States. The great majority of primary lesions appeared on the mucous membranes. Three patients first noted a persistent sore throat. One patient had oral lesions for two years before the development of cutaneous change. In 5 patients the disease had been present more than 1 year. No correlation was noted between the age of the patient and the duration of the disease.

The laboratory findings were meager. All patients presented a moderate anemia. Some eosinophilia was noted in all differential counts. It ranged from 2 to 11% in all but one case in which the eosinophilia was up to 40%. There was some reduction of the serum albumin in all cases but there was only a slight change in the albumin-globulin ratio.

Adrenal changes were found in 4 of the University Hospitals autopsies. The hospital record was checked in an effort to correlate these changes with clinical and laboratory findings. In one patient with Pemphigus Foliaceus, degenerative changes of the adrenal were found. On admission, her blood pressure was 120/70. The only blood chemistry recorded was a blood calcium level of 10 mg./100 cc. Five days later the calcium level was 6.0 mg./100. Treatment with calcium gluconate and dihydrotachysterol was administered until the time of death ten days later. The blood calcium was not rechecked.

In a second case, moderate autolysis of the adrenals was found at autopsy. In this 45 year old female the chloride level was 604 mg.% on admission. It was reported as 574 mg.% 3 weeks later and as 616 mg.% shortly before death. There had been no treatment to explain what little difference existed.

Within the past year, 7 cases of pemphigus have been treated at the University Hospitals. There was one death. An attempt was made to study this group more intensively. The peripheral blood was checked at frequent intervals. Other tests included bone marrow biopsy, serum sodium, potassium and chloride levels, fractional proteins, liver function tests and examination of the vesicle fluid.

The blood chloride level in this group varied from 556 to 628 mgm. per 100 cc. In only 2 patients was the level below 600 mgm. In one of these patients the chloride level remained around 560 both when he had many bullae and when his skin was perfectly clear. In the second patient the chloride level was 574 mg.100 cc. when his skin condition was at its worst. At the time of discharge the level was 620 mg. per cent. There seemed to be no relationship between the chloride level and the severity of the disease.

The sodium levels ranged from 311 (135 milliequivalents per liter) to 377 mg.%, (144.8 milliequivalents per liter). In our most severely ill patient with a very extensive process that left only small islands of normal skin, the sodium level was 324 mgm.% (140 milliequivalents per liter). The patient was extremely toxic at the time and had a generalized anasarca. His chloride level was 593 mgm. per 100 cc. at the

time.

Normal values may be seen even in the far advanced disease. Mrs. A.P., white female age 82, had a blood chloride level of 600 mgm. per cent and a blood sodium level of 315 mgm. per cent (135 milliequivalents per liter) just prior to her death.

The blood potassium level ranged from 15 (3.9 milliequivalents per liter) to 18 mgm.% (4.62 milliequivalents per liter). There was no correlation with the patient's general condition nor with the changes in sodium level.

Sufficient vesicle fluid was obtained from 2 patients for study. In one patient the chloride level was 630 mgm.%, the sodium 310 mgm.%, and the potassium level 20 mgm.%. At the same time the blood levels were as follows:

Chloride 631 mgm., sodium 331 mgm., and potassium 17.8 mgm. %.

In the other patient the sodium in the vesicle fluid was reported as 142 milliequivalents or 327 mgm. %. This was exactly the same as the blood sodium level determined on the same day. These findings are in contrast to those of Pitts and Johnson who reported the sodium potassium and calcium levels of vesicle fluid to be lower than that of serum.

All patients had varying degrees of anemia. The hemoglobin level seemed to drop as the pemphigus became more extensive and the patient more toxic. Repeated transfusions gave the necessary support.

In all cases the sedimentation rate was elevated, the extensively involved patients having a sedimentation rate that ranged up to 130 mm. in 60 minutes. The rate dropped as the cutaneous condition improved. The eosinophilia ranged from 4 to 16 per cent and bore no apparent relationship to the cutaneous condition. The bone marrow biopsies revealed in most cases only a marrow eosinophilia. In some cases the bone marrow was hyperplastic.

The greatest aberration was perceptible in the fractional serum protein determinations. In most cases the total proteins were reduced and there was a change in the albumin globulin ratio. Two patients exhibited a greater change in the ratio during the height of their illness. In one the albumin was 3.6 with a globulin of 4.2. The other patient had an albumin level of 2.2 with a globulin of 4.8. At the time of discharge the ratio approached normal with the albumin 3.7 and the globulin 2.9 grams per cent.

Liver function tests carried out in these 6 patients revealed no real evidence of impaired liver function. One of the patients showed a 15% retention of bromsulphalein in 45 minutes. The remaining tests showed no marked change.

The differential diagnosis of pemphigus should include: erythema multiforme, dermatitis herpetiformis, bullous lichen planus, the generalized vesicular eruption associated with lymphoblastomas, drug eruptions, bullous syphiloderm and bullous impetigo. The latter disease has frequently been referred to as Pemphigus Neonatorum.

Bullous impetigo, especially the form referred to as Pemphigus Neonatorum, is an infectious disease caused by staphylococci or streptococci. It is differentiated by the history of contagion and the auto inoculability of impetigo lesions. The bullous type of syphiloderm seen in prenatal syphilis has also mistakenly been called Pemphigus Neonatorum. It is generally limited to the palms and soles.

At times the differential between pemphigus and dermatitis herpetiformis is not easy and often impossible without prolonged study. In dermatitis herpetiformis the lesions are multiform at some time during the course of the disease.

Drugs such as iodides, phenobarbital and sulfadiazine can produce bullous eruptions that simulate pemphigus. The combination of the eruption plus the toxic picture of a drug eruption can make the diagnosis very difficult at times.

The severe form of erythema multiforme and Stevens-Johnson Symdrome may be one

and the same process. Either of the two conditions with the associated mucous membrane lesions may have the appearance of pemphigus in its acute phase.

Some comparison can be made between Lupus Erythematosus and Pemphigus. They are both systemic diseases and may have a fatal outcome. There is a toxic picture in each with elevation of temperature and cachexia. In acute Lupus Erythematosus the cutanecus changes are less pronounced, whereas in pemphigus the severity of the process is mirrored in the skin. Pemphigus does not exhibit the mesenchymal, cardiac, renal or pulmonary changes of Lupus Erythematosus. The similarity in the peripheral blood picture is only seen in the hypochromic anemia. There is leucocytosis rather than leukopenia as found in Lupus Erythematosus. Frequently one sees a change in the albumin globulin ratio but at least part of the decrease in serum albumin is due to the loss through the cutaneous lesions. Some degree of hyperglobulinemia, however, does occur in Pemphigus. There are no abnormal urinary findings in Pemphigus as compared to Lupus Erythematosus. What if any relationship the few similar findings indicate is impossible to say at this time.

Comments

In summary one can only say that pemphigus is a severe systemic disease with cutaneous manifestations. The severity of the disease varies with the type of cutaneous involvement. It is entirely possible that the various types listed are not divisions of a single disease but may be distinctive processes with similar cutaneous changes.

As yet the etiology of pemphigus has not been determined. When this mystery is uncovered more specific therapeutic measures can be taken. To date there is no single therapeutic measure that can be considered a consistently effective agent in the treatment of pemphigus. If convalescent serum proves to be of value it would at least emphasize the infectious character of pemphigus. This therapeutic agent is being given further trial here.

The autopsy findings in pemphigus are so meager that they give little or no information as to the underlying pathologic physiology. The blood changes in this disease indicate a disturbance in acid base balance as well as a shift in essential elements.

One might conclude with the statement that pemphigus is probably an illness caused by an infectious agent or agents as yet unknown which produce a disturbance in endocrine functions.

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