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Neurodermatitis : another skin mystery

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By

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INTRODUCTION

Neurodermatitis, although a clear-cut clinical entity, is a dermatologic disorder with numerous names and of unsettled etiology. It is referred to in the medical literature as chronic disseminated neurodermatitis, circumscribed generalized neurodermatitis, atopic dermatitis, localized neurodermatitis, lichen simplex chronicus, lichenification, and pruritis with lichenification. At present, the two most popular names are atopic dermatitis and chronic neurodermatitis and, as the terms suggest, each is employed by one or the other of the two principal schools of thought as regards etiology. In this thesis, the terms will be used indiscriminately.

Neurodermatitis, although still erroneously called a chronic eczema by many practitioners, first was mentioned in the literature over a century ago. Apparently the first to write on this entity was Robert Willan, an Englishman who, according to Alexander (1), in 1808 briefly discussed the disease and gave it the name lichenification of the skin. However, the first good description of neurodermatitis, removing it from the field of the so-called eczemas, was given by several Frenchmen in the latter part of the nineteenth century.

Vidal (2), in 1886, gave new impetus to the conception of the term lichen and suggested the name "lichen simplex chronicus." Brocq (3), in 1891, and with Jacquet (4), in 1896, reviewed these concepts and suggested the name "neurodermite," based on probable etiology and pathogenesis. Besnier (5), in 1892, introduced the term "prurigo diathesique" to lay emphasis on the constitutional factor in the disorder. Since then, neurodermatitis has been a subject of etiologic dispute, principally in American dermatologic circles, during the last two decades.

Clinically, the picture of neurodermatitis is well known and is approximately as Brocq (3) described it half a century ago. It is a chronic disease of children and younger adults producing plaque-like hyperpigmented lesions exaggerating the lines of the skin; sites of predeliction for the lesions are the antecubital and popliteal areas, the sides and back of the neck, the axillas, the shoulders and the thorax. Results from treatment are disappointing, irradiation giving best relief from itching--the most marked symptom. However, this disorder, for the most part, is self-limited, usually abating in middle life.

The principal problem in neurodermatitis, at present, is determination of etiology so that a satisfactory means

of treatment may be worked out. The purpose of this thesis is to review the literature, particularly as concerns etiology and treatment, and to present, criticize and evaluate the pertinent facts and theories. This disease was selected as a thesis subject not only because it is a common mysterious disturbance of the skin, but also because it concerns the role of atopic, neurogenic and metabolic factors in disease.

Consequently, the subject will be considered under the following main headings: etiology, pathology, diagnosis, treatment, and complications and variations.

ETIOLOGY

Neurodermatitis has been a controversial subject for several decades because of efforts to determine its cause. Until the waning years of the nineteenth century, neurodermatitis was considered nothing more than a form of chronic eczema, but about this time it came into clinical being through the work of French dermatologists. Vidal and his brilliant pupil, Brocq, with Jacquet and others made an extensive study of this disease and demonstrated that "neurodermite," as Brocq labeled it, could be differentiated easily from eczema.

Ever since this initial research, dermatologists have been striving to solve this etiological puzzle, but today the basic factors concerned in its development are still a mystery. There are two main schools of etiology; one holds it is in some way linked with instability of the nervous system, while the other argues it is an allergic reaction. For the most part, the findings and contentions of these schools will be presented in chronologic order.

Neurogenic Disorder?

In 1886, Vidal (2) discussed the lichens and prurigo and under the term "lichen simplex chronicus" distinguished a peculiar chronic condition of certain types of young people who suffered from irregularly occurring

episodes of paroxysmal pruritis followed by thickening of the skin, lichenification, excoriated papules and other manifestations involving circumscribed zones or widely disseminated over the body in characteristic location. He mentioned the association or alternation with asthma in certain cases, and spoke of a constitutional background consisting of an unstable nervous temperament in most cases. He advised treatment of topical remedies, sedatives, diet, and moderation of activities to prevent emotional and physical fatigue.

The terms "prurigo diathesique" and "neurodermite diffuse" were coined by Besnier (5) and Brocq (3), respectively, to lay emphasis on the diathetic or constitutional factor of the reactivity on the one hand, and on the essential nervous disposition on the other; pruritis was considered the primary symptom and the gross cutaneous changes as subsequent secondary manifestations in persons predisposed to the condition.

Brocq (3), who can almost be considered the "founder" of neurodermatitis, observed it occurred in neurotic persons and that excessive indulgence in condiments, tea, coffee, alcohol and tobacco were contributing factors. Although he associated the disorder with extensive itching and nervousness, Brocq, according to Taub and Zakon (6), apparently had no desire to imply

an immediate casual involvement of the central or peripheral nervous system; it is for this reason, perhaps, that in his later writings (7) he referred to the disease as "pruritis with lichenification." Nevertheless, Brocq still generally is given credit by most writers as fathering the idea that neurodermatitis is, in some manner or other, a nervous disturbance. It was also he who first strongly contended that neurodermatitis was not an eczema.

Incidentally, general acceptance of the view that neurodermatitis was not an eczema was far from immediate. As a matter of fact, even today many practitioners label neurodermatitis an eczema; however, this is more or less due to ignorance. Brocq really got his first staunch support in this matter from Americans. Heimann (8), in 1917, and Wise (9), in 1919, backed this view and criticized British and German schools for continuing to view this disorder as a chronic eczema; they pointed out that both grossly and histologically the primary type of neurodermatitis was a disease entity. From the late 1920's on, however, most authorities in this field agreed with Brocq, and the controversy has not been differentiation from eczema but the cause of neurodermatitis.

Both dermatologists and psychiatrists long have been aware of the influence of the patient's emotional state

on both the exacerbations and the chronicity of the illness, but great differences of opinion have existed as to the exact role of the emotional state. Neurogenic proponents point out the close embryonic relationship between the skin and the nervous system; both are derived from the ectoderm and retain a direct anastomotic connection with each other through the peripheral nerves. Through this connection, they contend, the skin can mirror disturbances of the nervous system.

Principal leaders in the neurogenic school are two Americans, Stokes and Becker, with their collaborators. Becker (10) entertains a dynamic concept regarding the nature of all the neurodermatoses, believing that "protoplasmic irritability" or unrest associated with an underlying constitutional defect makes for constant fatigue which, in turn, enhances this deficit. Stokes (11) stresses the underlying emotional factors in what he calls the psychoneurogenous component of the cutaneous reaction mechanism. Rogerson (12), an Englishman, emphasizes the occurrence of neurodermatitis in persons with a "vagotonic" background.

Becker (10), in 1935, gleaned his impressions from a study of 204 unselected cases of dermatoses, concluding

these conditions including neurodermatitis seemed to be found only in a certain type of person. He said: "The underlying constitutional background seems to be hereditary but not familial. Many of the patients fall into the so-called neurasthenic group with the picture of general asthenia and neurocirculatory instability. The constitutional symptoms are easy fatigability, nervous and mental irritability or depression, hyperkinesia, functional gastro-intestinal disturbances, headache, backache, vasomotor rhinitis and asthma."

Becker had no explanation for the mechanism of lesion production. The cause of pruritis, cardinal symptom of most dermatoses, is unknown, he related, although edema of the nerve endings was mentioned as a possibility. The dermatoses associated by Becker with neurocirculatory instability included generalized pruritis, localized pruritis, neurodermatitis, dyshidrosis, urticaria, angioneurotic edema, alopecia areata, lichen planus, dermatitis herpetiformis, and scleroderma.

In 1935, Becker and van de Erve (13) attempted to determine the personality and social status of patients with neurodermatoses. In a study of 80 patients, they observed that on the whole patients with neurodermatitis tend to drift into occupations requiring more activity

and responsibility than usual, that they were over-conscientious in performance of their duties. Success was found to be good as a rule, unless neurodermatitis or instability interfered. Becker again concluded these patients had been born with "generalized protoplasmic unrest," and asserted therapeutic measures directed toward relief of instability and exhaustion seemed to offer the best therapeutic promise.

Stokes in his earlier writings (14) observed, after a review of the literature, a comparative rarity of serious studies of the sexual psychoses as factors in the development and prolongation of dermatologic symptoms. He presented several cases in which he believed sexual psychoses were an element in the maintenance, if not the actual origin, of itching. He ventured the belief that primary pruritis may be an expression of an underlying sexual stress or craving.

Stokes (11) also stressed the psychosomatic concept of the "total personality" as a factor worth considering in the analysis of disease causation. He sought to place the personality of the person with neurodermatitis in some definitive relation to the behavior of his skin; again, not as a sole cause of his trouble but as a factor in a complex of hereditary, physiologic, allergic, bacteriologic, and immuniologic.

Stokes put neurodermatitis patients in two psychosomatic correlation groups: (a) eczema-asthma-hay fever personality, and (b) tension frame of mind. Patients in the first group he labeled with a temperament developing in the second, third, or even fourth generation descendants of nervously intense and high-strung allergic persons. Several generations of emotion-allergy combination produce a "diathetic" individual whose traits include a deep-seated feeling of insecurity, feeling of inferiority, aggressiveness, disposition to dominate, self-consciousness, marked lability of physical and mental reaction, an intrinsic kinetic drive, higher than average I.Q., tension and restlessness. Stokes asserted this makeup favors a tempestuous existence in which repercussion into the gastro-intestinal secretory and motor mechanisms, the endocrine and metabolic machinery, and the allergic state can be expected. While such a makeup may provide a basis for complexes in the technical sense, it is replete with basis for conflict, according to Stokes. His "tension frame of mind" personalities exhibited the basic sense of insecurity, rendered into fear of inadequacy, fear of failure and fear of not measuring up to a standard which is usually set at exaggerated performance levels by the same "I"-sensitiveness which

appears in the eczema-hay fever-asthma personality. Stokes asserted that conflict often winds up in a personality crackup.

Stokes (15) also has described an "office technique" of approach for detection and treatment of neuroses considered factors in neurodermatoses. He said the open type of tension is easily recognized by the fidgeting, constant movement and jerkiness of action and enunciation; the closed tension type is more difficult to detect because he hides behind a mask or "poker face" whose traits include the elevation of the chin, the throwing-back tendency and rigidity of the neck, the tense abdominal wall, the arched lumbar spine, and the thrust-out feet. Stokes also called attention to the vagotonic type with his clipped enunciation and heightened tone, the jerk that he gives to his shoes and shoestrings--all giving evidence of the high output of central energy constantly bombarding his peripheral structure. Appraisal of the vasomotor status also was stressed--the come-and-go of color, the flushing of the dermatologically involved areas under observation, the blueness of hands and feet in a dependent position, the blanching of flushed hand in elevation, red dermatographism, and abnormalities of the sweat mechanism.

However, Stokes and Becker are far from alone in propounding the neurogenic theory.

Heimann (16), incidentally, remarked in 1925 that neurodermatitis occurs in the neurotic type of patient, and that there was no question that the sympathetic nervous system, the vasomotor system, and so on, play an important role.

Rogerson (12) pointed out that the skin is one of the best organs of the body in which psychological changes can be demonstrated. He asserted "the blush of shame or embarrassment, the hot, dry skin of anger, the cold sweat of fear"--all are so well recognized in literature and tradition that it is strange to observe the reluctance of many patients to concede a psychogenic factor in their lesion. He explained symptoms of neurodermatitis may be produced entirely as a result of psychological conflict, by a combination of psychological conflict and organic determinants, or by organic factors, but maintained by psychologic factors.

Eppinger and Hess (17) first put forward the concept that there were two main types of patients in whom psychological disturbances were likely to play an important part in the production or aggravation of skin symptoms--the vagotonic and hypersympathicotonic types. The vagotonic they described as introverts with sallow complexion, bluish lips, thick skin with a tendency to

pigmentation, white dermographism; the hypersympathicotonics were pictured as extroverts, with a tendency to flush, red lips, red dermatographism, and rapid pulse.

Rogerson noted, however, that more recent writers have tended to put less stress altogether upon these two types and more upon the fact that many patients show signs of disturbance at the vegetative nervous level which are not easily divided into one or the other type. Becker said his neurocirculatory instability included both types.

Tilliam and Squires (18), in 1941, found that many neurodermatitis patients needed psychiatric attention; that many were unaware of the mental factor in the causation of their skin disorder. These authors used hypoglycemic reactions, produced by insulin, in the successful treatment of five neurodermatitis patients; repeated shock treatments produced apparent relaxation and diaphoresis and relieved symptoms.

They contended emotional tension and mental depression profoundly affected the functioning of the autonomic nervous system, and were capable of producing trophic and pigmentary changes in the skin, probably through the effect on the glands of internal secretion and/or the vasomotor system. In agitated and depressed

patients it was their usual experience to find a dry, sluggish skin which, in protracted illness, would show some degree of trophic change. Tilliam and Squires asserted neurodermatitis may be considered a symptom of internal disturbance.

Greenhill and Finesinger (19), in 1942, studied 32 patients with neurodermatitis to evaluate the influence of emotional factors on the disease. They were investigated by means of questionnaires which embraced the dermatologic, medical and psychiatric history, the presence of neurotic symptoms, and the personality characteristics of each patient. Controls included 16 patients with lupus erythematosis, 20 psychoneurotics, and 20 normal persons. Neurodermatitis patients showed psychoneurotic symptoms, particularly phobia and compulsive-obsessive tendencies, more frequently than any of the others except the neurotic group itself. The neurodermatitis victims also were found to have a higher incidence of hostile tendencies, feelings of inadequacy and depressive trends, although blushing and exhibitionism occurred no more prominently. These authors concluded there was a definite correlation between events which evoked feelings of anger and depression, and exacerbations of the eruptions in patients with neurodermatitis.

Atopy?

This newer concept on etiology has been advanced by such recent authors as Rost, Sulzberger and his collaborators, Coca, Hill, Taub and Zakon, Wise and Wolf and many others. They consider a specific vascular skin hypersensitivity to foods and/or to environmental allergens to be the essential factor in the production of disseminated neurodermatitis. They, led by Coca and Sulzberger, have substituted the name atopic dermatitis for neurodermatitis.

However, the possible connection of neurodermatitis with allergy was noticed way back in 1886 by Vidal (2) who mentioned the disease was associated with asthma in certain cases. Rasch (20) in 1915, Hauxthausen (21) in 1925, and Low and Drake (22) in the 1928 British symposium pointed out the close association with infantile eczema, asthma and hay fever and the reactivity of the skin to specific proteins, particularly as they applied to the condition in children up to the time of puberty.

Wise (19) in 1919 mentioned the possibility a foreign protein sensitization might be the cause of the trouble.

Rost (23) introduced in 1930 the descriptive phrase "eczematoid with early and late varieties,"

considering the late variety to affect persons between the ages of 15 and 30 whose condition represented a tardive phase of the exudative diathesis. In a recent article Julg (24) contended that there was no justification for such a separate distinction apart from the broad classification of "allergic eczema on a constitutional basis."

In this country in the 1930's, Coca and Sulzberger stimulated interest in and studied allergic phases of neurodermatitis. In 1934 Coca (25) elaborated the thesis of atopy to express the peculiar hereditary capacity of certain human beings to manifest untoward reactions to common protein materials, with the development of asthma, hay fever and sometimes eczema. He believed dermatitis patients must be classified either as an atopic dermatitis due to antigens or as a contact dermatitis which is not due to antigens. He believed a multiplicity of antigens was involved in many cases and that antigens could be inhaled as well as ingested. He observed that patch tests were positive in contact dermatitis, negative in neurodermatitis, whereas scratch and intradermal tests usually were positive in neurodermatitis. Coca cited as an example a typical

neurodermatitis case, with positive scratch and intracutaneous tests for wheat flour, whose lesions vanished when he did not eat wheat derivatives but returned when he did.

Wise and Ramirez (26) in 1925 noted many patients did not react to proteins but a sufficient number did and were improved by removal of offending allergens; they also observed the relationship between neurodermatitis and asthma and got positive tests to food, pollens and animal emanations in many cases. They speculated it might be possible to divide neurodermatitis into allergic and non-allergic types.

Hazen (27) in 1928 called neurodermatitis an allergic disease but listed irritability of the nervous system along with fur, powder, wheat, and dust as a form of allergen.

In 1932 Sulzberger with Spain, Samnis and Shahon (28) reported that reagins (antibodies) to food and inhalants could be demonstrated in most of their neurodermatitis cases, although there usually was a polyvalent hypersensitivity. They also noted a high positive family allergy history and observed many of their cases had had infantile eczema. They also noted that contact dermatitis had positive patch tests, that in neurodermatitis patch tests were negative and scratch

and intradermal tests were positive.

Taub and Zakon (6) in 1933 disclosed observations in 14 cases which favored placing neurodermatitis in the class of allergic dermatoses. Their findings were typical: positive allergic history, many had other allergic conditions, typical skin test reactions, normal basal metabolic rate, and normal blood calcium and phosphorous levels and blood count and urine findings.

Biberstein and Frohlich (29) joined the allergic school of thought in 1932 as did Urbach (30) about this time.

In 1934 Sulzberger and Vaughn (31), using the Prausnitz-Kustner test for antibodies, demonstrated that two typical cases of neurodermatitis were due to inhalation of silk--that wearing silk caused skin flareups not at the point of contact but at the usual neurodermatitis sites. They also asserted that penetration of allergens through the intact epidermis was possible but not very rapid, explaining why patch tests usually were negative in neurodermatitis. However a year later Sulzberger and Rostenberg (32) acknowledged the specific etiologic agents in a particular case often were impossible to ascertain; they said skin tests were in most cases of limited usefulness because

of the demonstration of many antibodies, thus making it impossible to eliminate all the possible causitive factors.

Sulzberger and Goodman (33) in 1936 reported results of a careful study of 50 neurodermatitis patients, asserting they could find no convincing evidence of the primary importance of psychoneurogenic factors in the production of the dermatitis. They held the family and personal history and the course and results of investigations and therapy demonstrated that the dermatosis was associated closely with diseases of the atopic group. Their observations "strongly" suggested that specific skin hypersensitivity was in many cases an important factor in the production of atopic dermatitis. They admitted, however, that while in many cases the adduced evidence suggested specific skin hypersensitivity as the cause, unequivocal proof still was lacking.

However, Sulzberger and Goodman insisted "nervousness" was coincident, concomitant, and the result of normal reaction to a dermatosis. In their cases they often were unable to determine cause of fluctuations but the patients blamed heat or cold, rapid temperature changes, certain foods such as fish or eggs, specific

articles of clothing, greases or greasy ointments, work, worry, nervous strain or upsets. Remissions often were produced by changes in environment or intercurrent infection. However, they pointed out, environmental change or intercurrent infection often were beneficial in asthma, hay fever, and infantile eczema.

Hill (34) in 1934 published some interesting observations in chronic atopic eczema in childhood. He said the disease began in infancy, often improved with age and even disappeared during the second year. In 900 cases in infants and young children he reported eczema occurred in 210 between the ages of two and 12, in 127 it had persisted since infancy, and in 83 it appeared after the second year. The clinical picture was very similar to that of atopic dermatitis in adults. Hill called the disorder atopy because reagins were found in the blood, because it usually gave skin tests similar to those in adult atopic dermatitis. Incidentally, proved allergens included eggs, cat hair, wheat, spinach, and milk. However, he admitted there was no good answer to the atopic problem as yet--even with demonstration of allergens.

Hill and Sulzberger (35) a year later concluded

infantile eczema was a part of atopic dermatitis and outlined three stages of the disease--infancy, childhood and adulthood. They held in infancy the dermatitis was due to hypersensitivity to "protein" substances, that if it persisted throughout childhood or adulthood it was known as atopic dermatitis. The immediate exciting agents may vary at different age periods but the fundamental predisposition which makes the development of the dermatitis possible was the same at all ages, the authors pointed out. They admitted, however, that in many cases there were undoubtedly other factors than atopy at work of which practically nothing was known.

Osborne and Walker (36) agreed substantially with Hill and Sulzberger. Their investigations in 1938 of contact and environmental allergy in childhood eczema brought a high per centage of satisfactory results. Although there was no experimental evidence that a person inherits any specific epidermal hypersensitivity, they held he does inherit an "ease of susceptibility."

Brunsting (37) reported in 1936 on a study of 101 selected cases of atopic dermatitis affecting adolescents and young adults, noting a high personal history of hypersensitivity and a high incidence of

eosinophilia (14.8 per cent). Incidentally, eosinophilia is commonly associated with most allergic conditions. As a rule, Brunsting found health to be good with apparent endocrine function and blood pressure normal. He commented on the interrelation of pruritis and emotional upset but remarked that tangible criteria for the estimation of disturbance of nervous balance do not exist. He concluded:

"When one surveys the material from the point of view of evidence rather than speculation, one must admit that while the instability of the vasomotor system may be a contributory factor, especially in the cases of more severe disturbances, it is subordinate and probably secondary to a background of specific hypersensitivity."

Cleveland (38), who prefers to call the disorder lichen simplex chronicus, analyzed 170 cases in 1936, concluding the neurogenic factor did not occur with sufficient frequency to justify regarding the disease as a cutaneous neurosis. Consideration of the proportion of cases occuring in various occupations did not show that it affected chiefly persons with a high nervous organization who are correspondingly reactive to nervous and psychic stimuli.

Pels (39) believed this disease, more so the diffuse rather than the circumscribed type, might have

an allergic background. He acknowledged causal agents still were obscure, however. Rattner (40) by the way frowned upon the neurogenic idea, but ventured no other guess as to possible cause.

Wise and Wolf (41) lined up with the atopic school in 1938. Their studies gave findings similar to those already mentioned as regarding family and personal history and demonstration of antibodies and polyvalent hypersensitivity. However, they conceded there was no unanimity of opinion regarding the existence of antibodies, that the mechanism of sensitization was unknown, and that the matter of inherited predisposition was unsettled.

In 1944 Sullivan and Evans (42) asserted it was an "established fact" that disseminated neurodermatitis was due in part to, or at least associated with an abnormal allergic state. They concluded authoritative evidence was heavily in favor of regarding the phenomenon of hypersensitization as an important factor in the disease. Changes in personality they too attributed to prolonged discomfort, pain and embarrassment.

Meanwhile, the importance of inhalant atopens was stressed by Feinberg (43) in 1939; he claimed their neglect might be a reason therapeutic manage-

ment based on allergic findings had been disappointing. Feinberg proposed that the inhalation of fungus spores might be a factor in atopic dermatitis. He had 14 cases with a seasonal aggravation due to inhalation of pollen and fungi, basing this on skin tests, reagin demonstration, and correlation of intensity of symptoms with air content of pollen and fungus spores.

However, the inhalant atopy possibility had been mentioned many times previously. In 1918 Walker (44) reported four cases of eczema due to inhalants, two to horse dander, each each to timothy pollen and ragweed pollen. In 1921 Engman and Wander (45) described two cases due to horse dander, while Hazen and Whitmore (46) listed a case due to the same allergen four years later. Cohen and his associates (47) in 1930 demonstrated that pollen inhalation by passively sensitized subjects resulted in reactions at sites of sensitization. In 1933 Taüb and Zakon (6) believed hog hair may have been a factor in a case. Figley and Parkhurst (48) reported in 1935 five cases due to silk, demonstrating silk allergens in each case; incidentally patch tests were all negative. Sulzberger and Vaughn (31) by the way demonstrated

that silk allergens could be absorbed by inhalation in sufficient quantities to affect passively sensitized sites.

Netherton (49) in 1939 analyzed 50 cases of atopic dermatitis, 48 reacting to cutaneous tests with inhalants--dust, silk, orris and feathers. Incidentally Netherton also detected a polysensitivity, and expressed the belief these patients became tolerant to one allergen only to fall victim to another.

As regards seasons, Wise and Wolf (41) spoke of frequent exacerbations of the disease in the fall. Sulzberger and Goodman (33) also said most of their fall exacerbating cases were positive wheal reactions to ragweed. Cazort (50), in a paper dealing with relation of allergy to house dust, mentioned a case of neurodermatitis aggravated by oak pollen.

Endocrine Aspects

Contrary to what might be expected, endocrine disturbances have not received much attention as a possible cause of this dermatitis. Besnier (5) in 1892 considered neurodermatitis to be a "morbid property" of the individual. Engman (51) from 1912 to 1917 studied the possible relationship of thyroid dyscrasias to neurodermatitis, noticing that in some

of his cases there was evidence of mild hypothroidism while in others the tendency was a slight elevation in the basal metabolic rate. He conceived of a possible cutaneous fraction in the thyroid hormone complex which might affect cornification. Kendall (51) cooperated with Engman in his work at that time and furnished "thyroid B", a by-product obtained in the preparation of thyroxin. Engman used this substance therapeutically in a number of cases of neurodermatitis with occasional dramatic success. This work was interrupted by the war; Engman stated there was sufficient clinical evidence to warrant further endocrine investigation in this field.

Becker and Obermayer (52) in 1940 said basal metabolic rates in 142 dermatoses showed a hypothyroid tendency--out of 65 cases, 50 were hypo with an average of minus 12 while 15 were hyperthyroid with an average of plus five. Some of these patients received thyroid but Becker and Obermayer said no improvement was observed. Wise (77) also reported thyroid of no therapeutic value.

Mineral Studies

MacCardle, Engman and Engman, dissatisfied with

attempts to explain neurodermatitis on either an allergic or neurotic basis, obtained biopsy specimens from 33 neurodermatitis patients, 83 normal people, and 55 patients with other cutaneous diseases. Their studies have been among the most exhaustive and tedious in the history of the disorder.

By spectographic analysis in 1941 they (53) found the whole skin of neurodermatitis patients lacked magnesium and usually contained larger amounts of calcium than did skin from normal persons. Unaffected skin from the region of the midaxillary line and skin from active lesions and from healed lesions contained less than half the amount of magnesium found in skin of normal persons. In other inflammatory diseases of the skin, the authors reported, the skin usually contained large amounts of magnesium. In lichen simplex chronicus, the cutaneous lesions contained normal amounts of magnesium and in some cases excess amounts.

These investigators reasoned the skin magnesium deficiency was not the result of low magnesium diet since the food and blood serum of these neurodermatitis patients contained sufficient quantities of

magnesium. The skin apparently does not retain or accept biologically essential amounts of magnesium, they concluded, but whether the deficit was in the skin itself or in the blood vascular system could not be determined. Incidentally, the skin content of zinc, copper, phosphorus, aluminum, manganese, iron, boron, silicon and strontium also was observed spectrographically.

MacCardle and Engman (51) later put white rats on a magnesium deficient diet; the animals developed a reddening of the skin, exudative lesions and hyperirritability. Histologically the investigators found the rat skin lesions similar to those found in man but mineral changes revealed by microincineration were not alike. An enlargement of the thyroids with general calcification and fibrosis also was noted, possibly indicating a relationship between magnesium and calcium metabolism. Some of these magnesium-deficient rats were given anterior pituitary extract but no definite conclusions were reached.

Stimulated by this work, Sullivan and Evans (43) also created a magnesium deficient diet in rats. They found that both macroscopically and microscopically and chemically the lesions were different from those

of human neurodermatitis.

Engman and the MacCardles (54) also made micro-incineration studies in their series of cases, discovering the ash of unaffected skin from neurodermatitis patients differed from that of skin from normal persons. Most of the spinous cells in neurodermatitis skin were reported to contain much less white ash of calcium and magnesium than do normal spinous cells, while the remainder of the spinous cells had much greater amounts of white ash than do most normal spinous cells. The authors believed a small number of these spinous cells in the living state must have been overloaded with calcium and magnesium, while the majority of them must either have lost their elements or have been unable to absorb them. This loss and recovery of magnesium and calcium in the spinous cells of neurodermatitis skin, these men said, was probably a fluctuating process that occurred constantly, and an active lesion developed perhaps only when a certain large per centage of spinous cells had lost their elements.

In an active lesion the spinous cells of the epidermis were considered to have lost both calcium and magnesium, for their cytoplasm contained scarcely any white ash. Nearly all cells of the epidermis, including many of the basal cells, seemed to have lost intra-

nuclear silicon. It was difficult to determine whether these ash-poor cells had lost large amounts of their magnesium and calcium, or whether they simply had become disorganized to such an extent that they were unable to absorb biologically sufficient amounts of these elements. In incinerated skin from healed lesions, the large spinous cells were found to be hyperpigmented with white ash of calcium and magnesium, and there was silicon present in nearly every nucleus. This indicated to the scientists that the epidermis recovered these elements during the healing process.

In localized neurodermatitis or lichen simplex chronicus, Engman and the MacCardles reported the ash residue of active lesions differed markedly from that of chronic disseminated neurodermatitis in that there was a mobilization of calcium and magnesium to the spinous cells rather than a loss of these elements.

Histamine?

Liberation of histamine also has been suggested as being a possible cause of neurodermatitis. Stokes and Pillsbury (55) speculated on this in 1930, mentioning the gastro-intestinal tract as a possible

source.

Williams (56) made a study of this possibility with intramuscular injection of histamine in neurodermatitis patients; in 1938, he reported this produced an increase in the skin temperature at the site of predeliction for this skin disorder--the face, neck, flexures and so forth. In normal persons he noted a skin temperature increase limited to the face and neck and not the flexures. This suggested to Williams that the increased reactivity of these sites to histamine might be a factor in the characteristic location of neurodermatitis. However, he had no explanation for the mechanism of lesion production, except that histamine caused a dilatation of blood vessels and increased their permeability. He pointed out that the cardinal symptoms of neurodermatitis--pruritis, erythema and edema--were those elicited by the introduction of histamine into the skin.

Where histamine comes from is not known. Some claim it normally is present in the skin. Dale (57) and Lewis (58) suggested histamine may also appear in the skin of the allergic individual through the interaction of specific antibodies present in the endothelial cells lining the blood vessels of the

cutis when the specific antigen, which may be egg, wheat, milk, etc., is carried from the gastro-intestinal tract or lungs by way of the blood to these cells.

That histamine, or a histamine-like substance, can be liberated by an allergic reaction has been demonstrated by Horton, Brown and Roth (59) in the case of cold allergy.

Incidentally, Ehrmann (60), in 1924, concluded various forms of autointoxication, especially the intestinal absorption of protein split products, disturbances of pancreas, anacids, and hyperacidity of the stomach were factors.

Williams said it was possible that excessive scratching of an area of neurodermatitis, which is followed by urticarial thickening of the part, also may result in liberation of sufficient histamine to produce systemic effects such as are noted after intramuscular injection of histamine.

In 1939, Laymon and Cumming (61) reported on the use of histaminase in the treatment of neurodermatitis. Histaminase, which counteracts the action of histamine, was given to eight neurodermatitis patients during a month's trial, and in none was there

enough improvement to warrant giving any credit to histaminase. Smith and Hughes (62), in 1941, reported therapeutic trials with histaminase, in doses from 30 to 45 units, and found it "not altogether unsatisfactory," but commented more work was indicated.

Physical Allergy?

In 1925, Duke (63) reported what he termed "physical allergy." He said symptoms of bronchial asthma, vasomotor rhinitis and conjunctivitis, photophobia, erythema, pruritis, urticaria, angioneurotic edema, and eczema could be caused in some patients specifically and solely by action of a physical agent such as light, heat, cold, mechanical irritation, freezing and burns; usually one agent was responsible, heat being the most common cause. Some reactions were local, others distant. Duke speculated it might be a histamine reaction; he later (64) suggested the cause of these conditions might be a disorder of the heat regulating mechanism.

Tannenholz (65), in 1933, presented the case of a carpenter, 48, who had a flareup of neurodermatitis sites when exposed to heat. On putting a heat lamp to the patient's back, it became red in 15 minutes and an almost healed neurodermatitis lesion on the wrist

flexor surface became inflammed and exudative.

Miscellaneous

In 1941, Heyerdale and Cannon (66) reported the case of an obese woman with neurodermatitis of the legs of ten years' duration. On physical examination, palpable varicosities were found deep in fat on thighs and legs. Injection of the veins promptly cured the neurodermatitis.

Comment

A careful survey of all the pertinent literature on the etiology of neurodermatitis clearly shows that a satisfactory explanation of its pathogenesis does not exist. Both the neurogenic and atopic proponents can present interesting theories but proof is lacking; as a matter of fact, both groups will admit their arguments have shortcomings and that the final answer has not yet been reached. Experiments with the endocrines and histamine have been interesting but not enlightening. The careful work of MacCardle and the Engmans has revealed pertinent facts, but as yet has led to no new conclusions as to etiology; further research on mineral metabolism may provide better clues, however.

PATHOLOGY

As to the pathologic picture, dermatologists are much closer to complete agreement. The gross pathology was described most aptly by Brocq years ago. As regards the microscopic picture there is not complete accord but only relatively minor points are controversial.

Macropathology

As just mentioned, neurodermatitis presents a clear-cut gross pathologic appearance, and descriptions written in the late nineteenth century are almost as complete as those detailed today. Consequently it is appropriate to present in detail Brocq's original views in this connection.

Brocq (3) discussed two types of neurodermatitis--a primary and secondary form. The primary he regarded as a distinct disease entity with preeruptive pruritis followed by lichenification; the secondary he considered a lichenification frequently associated with many of the itching dermatoses, such as eczema, seborrheic dermatitis, mycosis fungoides, and pityriasis rubra. A translation of Brocq's views was made by Wise (67). In discussing the primary type, Wise quoted Brocq thus:

"At the outset, there is absolutely no visible lesion on the part of the integument; gradually the tissues change as the result of scratching; they first lose their normal color and assume a slightly dusky and at the same time pinkish tint. On close inspection, the skin is seen to present a finely granular and mottled appearance. At this stage it is already possible to discern in certain localities, under varying illumination, a sort of flattened, poorly outlined, somewhat glistening, very minute pseudo-papule formation. Later on, these lesions become more pronounced, the tissues assuming a dusky red color, or become distinctly pigmented; they are roughened or begin to be furrowed by fine criss-cross lines. The dermis gradually thickens, becomes infiltrated and the disease finally assumes a truly pathognomonic appearance.

"Having reached its stationary stage, circumscribed pruritis with lichenification has the general form of a more or less extensive patch of variable dimensions, but having an average diameter of five to 15 centimeters in its greatest axis. The outline is extremely variable, according to the case and the affected region, although usually of oval shape; it

may also be cresenteric, semicircular, or irregularly triangular. It may develop on any part of the body surface. These patches may be single in a given subject and always remain single; they may be multiple, very often two or three in number. Sometimes they are symmetrical, especially when situated in the flexures. When a patch has reached a quiescent stage, it sometimes presents three somewhat ill-defined zones: (a) a somewhat diffuse, pigmented external zone, velvety as if composed of fine very minute papules varying from light cafe au lait to light brown color; (b) a middle papular zone with lesions which are scattered toward the external boundary and confluent toward the internal boundary, being apparently formed by a much more papillary hypertrophy than that which characterizes the preceding zone, and (c) thirdly, an internal infiltration zone of more or less uniform appearance, in which the area is hardened, thickened or furrowed by a rectangular or lozenge-shaped criss-cross design.

"In secondary pruritis with lichenification, we deal with practically the same conditions with this important exception--instead of the patch being preceded by pruritis affecting an apparently normal skin, the lichenification is superimposed upon an

already diseased skin which itches and which the patient consistently scratches".

Wise (9, 26, 41, 67), who in 1919 and often thereafter stimulated American interest in neurodermatitis, was in accord with Brocq's findings, particularly the existence of primary and secondary forms. Wise (67) included in the primary type the lichen simplex chronicus of Vidal.

Sulzberger and Goodman (33) described the primary dermatologic lesion as a papule or a number of confluent papules forming lichenified areas. In uncomplicated cases, they found no vesiculation but noted weeping, crusting and exudation resulting from superimposed external irritation and infection. They stressed that the lichenified plaques were not very sharply demarcated, varied in color from a bright pinkish red to tan or dirty grey brown, and usually were surrounded by outlying, scattered and often excoriated papules. No skin area was found by these authors to be immune; while eruptions often were symmetrical, they were never zoniform, segmentary, systematized, or in any way distributed along the course of cutaneous or other nerves.

Cleveland (38) paid particular attention to sites

of lesions in reviewing 170 cases. In sites of single or symmetrical involvement, he reported 83 cases in which the disease was in 18 different areas. The nucha was the most common site, involved in 24 of the 83 cases. The other single sites were shin, sides of neck, scalp, inner and outer sides of the thigh, palm, antecubital space, gluteal cleft, perineum, popliteal space, flexor surface of forearm, extensor surface of forearm, labium majus, sacral area, clavicular area, knee, groin and forehead. In sites of multiple involvement, the nuchae, sides of neck and popliteal areas were most numerous. Next in order were shin, extensor surface of forearm, perianal region, inner side of thigh, flexor surface of wrist, thoracic wall, palm, scrotum, anterior axillary fold, dorsum of hand, face, pubis, outer side of leg, scalp, sacrum, calf, flexor surface of forearm, retro-auricular region, labum majus, abdominal wall, anterior surface of thigh, outer surface of thigh, knee, buttock, ankle, sole, hip, and dorsum of foot.

Among the atopic school supporters, infantile eczema is considered one of the early forms or precursers of atopic dermatitis. Sulzberger and Hill (35) described atopic dermatitis in three stages:

first, as in occurs in infancy; second, in childhood, and third, in adulthood. A description of these stages follows:

First--begins as papulovesicular rash on cheeks, soon extending elsewhere to outer aspects of lower legs, forearms, wrists and forehead. It may not always be vesicular; it may be flattened and scaly. There often are irregular areas of erythema, exudative papules being the most characteristic. Scratching may give rise to punctate appearance. As patients grow, new sensitizations may develop and those had in the beginning are lost; important atopens are egg, wheat and milk in the food group and silk and cat hair in the environmental group.

Second--occurs from two to 12 years, the common sites being those already described for adult neurodermatitis with typical appearance. There is no vesiculation and itching is intense.

Third--develops with exacerbations through childhood or may appear in adolescense after remission since infancy. The skin lesions already have been described.

Sulzberger and Hill concluded that, although chronic with remissions, the disease usually runs itself

out because the patient outgrows the sensitiveness. They based this belief on the fact that during a ten-year period they saw only one case in a patient over 35 years.

Becker and Obermayer (52) described two types of neurodermatitis--the dry and wet. The dry form is similar to the primary type of Brocq. The wet form differs both in location and nature of lesions; the flexor surfaces of the elbow and knee never are involved while most common sites are back of fingers and hands, dorsum of feet, extensor surface of the legs and face. If the lesions extend to the thickened portions of the hands and feet, they are dyshidrotic but without vesicles.

Becker and Obermayer's wet lesions are sharply circumscribed plaques, less erythematous than the dry type with no vesiculation, but with considerable exudation and serous crusting. The course differs from the dry type in rapidity of appearance and disappearance. While the dry type starts with itching and mild dermatitis and later becomes lichenified, the wet lesions originate quickly with slight erythema and exudation and often disappear just as quickly under treatment. The skin rarely becomes thickened or shows changes resembling lichenification; the pruritis is

not as severe. If the face is involved, the eyelids always escape.

Micropathology

The histopathology in neurodermatitis also was worked out long ago. Brocq and Jacquet (4) in their 1896 report on the disease noted hyper and parakeratosis, acanthosis, vascular dilatation in the papillary body, and islands of proliferated connective tissue cells. Incidentally, hyperkeratosis means hypertrophy of the corneous layer of the skin; parakeratosis is any abnormality of the corneum, and acanthosis stands for thickening or hypertrophy of the prickle-cell layer.

Jacquet (4) emphasized a lymphatic dilatation in the cutis with edema of the collagen, largely retracted to the perivascular areas in the papillae; in the epidermis he noted alteration cavitare, a normal granular layer, and the presence of migrated leukocytes.

Also agreeing on these salient features were Kreibich (68), Ehrmann (60), Alexander (1), Fick (69), and Heimann (8); Heimann listed these as: parakeratosis and hyperkeratosis with intercellular edema of the rete pegs; acanthosis in the rete pegs causing

an elongation of the latter; subepidermal accumulations of serum; hypertrophy and edema of the papillae; dilatation of the capillary vessels; infiltration of the papillae with lymphocytes, fibroblasts and a few mast cells. He stressed as negative features the absence of these conditions: vesicles in the epidermis; fat in the epidermis, vessels and skin glands; follicular involvement, and disturbance of pilosebaceous organs.

The primary site of reaction in the skin is a point of controversy. Up until the time of MacCardle and the Engmans (70) in the early 1940's, nearly all authorities in this field considered the initial reaction to be in the derma; however, this trio put it in the spinous cell layer of the epidermis. Brocq, Jacquet, Kreibich, Heimann and other early writers mentioned dermal changes in their discussions of histopathology. Alexander (1) and Gans (71) were among the first to point out specifically that because of the perivascular infiltration the primary reaction was centered in the cutis around the blood vessels with secondary changes in the epidermis. Block (72), Sulzberger and cohorts (73), Becker and Obermayer (74, 52), and Coca (25), among others, also have pointed to the derma.

MacCardle and the Engmans drew their conclusions from their exhaustive study of the series of patients already mentioned. Because their work is the most recent, their claims will be presented in detail as follows:

At the outset of neurodermatitis, the skin, at the site of future lesion in the affected area, is undoubtedly similar to the unaffected skin elsewhere in the body where lesions never occur. The same sort of processes as occur in areas of active lesions also occur in the unaffected skin in the region of the mid-axillary line, but to a less conspicuous degree. The preliminary site of the developing lesion is highly pigmented in most places and hyperkeratotic in non-pigmented areas. The non-pigmented areas are probably the most vulnerable ones. There is an unusual amount of perivascular infiltration, although the caliber of the blood vessels is normal. The epidermis is slightly acanthotic, especially in non-pigmented areas. The intercellular fibrils and then nucleoli are heavily keratinized in areas of hyperkeratosis. The spinous cells are larger than normal spinous cells.

The first reaction, according to these authors, is probably a change in the chemical constituents of the spinous cells, which results in the keratinization of

of the intercellular fibrils and of the nucleoli. Such a change might be conceivably traced to the blood vascular system, since there is considerable perivascular infiltration. The perivascular infiltration is most conspicuous in the non-pigmented areas. Perhaps excess amounts of gluthione were supplied to the epidermis and the basal cells were unable to bind it into melanin. Its components may, therefore, have damaged the spinous cells immediately above them, causing not only hyperkeratinization but also imbalances in mineral constituents. It is difficult to localize the primary shock tissues in neurodermatitis, since so many deviations from the normal structure appear in the same tissue. Any explanation of them for the present remains hypothetic, they argued, because a complete chronologic story is lacking.

The earliest lesion these men were able to obtain was completely depigmented. The rete pegs were slightly elongated, and there was little evidence of edema. In the later active lesion, the epidermis was much more thickened; the rete pegs were elongated, and the dermal papillae were distended by edema. The hyperkeratinization had reached its peak of activity and most of the blood vessels were dilated with some parts of their walls imbedded in lumps of lymphocytic infiltrates.

Clumps of infiltrated white blood cells were limited to the vessels near the apices of the rete pegs and were absent in the dermal papillae.

The second stage of the developing lesion MacCardle and the Engmans described as consisting of a thickening of the epidermis by acanthotic processes and by hypertrophy of individual cells, and of a decided deposition of keratin, formed as a result of the dissolution of an excess amount of pigment. The last process that occurred was the thinning and ultimate breakdown overlying the emedatous papillae. After this there was a mobilization of certain clear cells which probably acted as phagocytes, melanoblasts, and particularly, regenerative cells to supply a new epidermis. Hyperpigmented patches developed, and much of the corneum became parakeratotic and hyperkeratotic alternately. This temporary and fluctuating condition then persists probably until the next attack.

To these scientists, it seemed that the clear cells were more frequently related to the regeneration of the new epidermis than to any other physiologic phenomenon, for in recently healed lesions that showed large numbers of faintly stained mitotically dividing basal and spinous cells, the clear cells could be seen

dividing in the basal layer. Many clear cells were found in any area of neurodermatitis skin where active mitosis and thickening of the epidermis was occurring. Clear cells in normal skin did not closely resemble those in pathologic skin.

Since MacCardle and the Engmans published their findings, issue has been taken on certain points by Ormsby and Montgomery (75). They contended lichen simplex chronicus and generalized neurodermatitis often cannot be differentiated microscopically; they also disputed the trio's finding that in lichen simplex chronicus the basal cell layer of the epidermis almost always consisted of a double row of cells that were piled on one another, and that the basal cells had huge nuclei twice the size of basal cell nuclei of disseminated neurodermatitis. They also questioned the statement that in generalized neurodermatitis the presence of large clear cells which they found independent of pigment activity, in fact were prominent in non-pigmented areas, and that this suggested there may be different types of clear cells and that they may not be epidermal in origin or be related to pigment formation.

Comment

The pathologic picture in neurodermatitis is not confusing. The gross appearance is fairly typical and easily recognized. The essential microscopic features also are clear cut, although MacCardle and the Engmans have taken exception of the previously assumed fact that the primary tissue reaction is in the derma; they contend this occurs in the basal cell layer of the epidermis. They also hold that lichen simplex chronicus is not a form of neurodermatitis, whereas most other authorities, including Ormsby and Montgomery, consider that it is.

DIAGNOSIS

Diagnosis of neurodermatitis is fairly easy because the clinical picture is quite typical. And this picture already has been described in detail, consisting of typical lichenified, pigmented patches found in such locations as the flexures, antecubital and popliteal spaces, the front and sides of the neck, and so forth. It is a disease primarily of children and younger adults, is a chronic disorder with remissions and exacerbations, and has as its principal symptom a severe itching either continuous or in crises.

Sulzberger and Goodman (33) found the average age of their patients to be 19, a typical case over 50 being rare. Cleveland (38) reported the disease slightly more common in women, three times more often in brunnettes than in blonds, and more frequently in Japanese and Chinese than in people of European origin.

Laboratory procedures are of some aid in diagnosis. As has already been stated, patch or epidermal tests are negative and scratch or dermal tests are positive to one or many foreign proteins. Skin testing is not too conclusive, however, as has been observed by Obermayer and Becker (74), Sulzberger et al (28), Coca (25), and others. Incidentally, an eosinophilia often is

found, Goodman and Sulzberger (33) detecting it in 25 of 50 neurodermatitis patients.

Other positive diagnostic findings might include nervousness or emotional irritability and family and personal history of allergy.

Differential diagnosis should not be too difficult. According to Cleveland (76), eczema, psorias, lichen planus, scleroderma, and seborrheic dermatitis need to be ruled out. Differentiating features in these disorders are as follows:

Eczema--vesicular and exudative, inflammatory, polymorphic character, usually small, red acuminate papules, positive patch and negative scratch tests, and distribution atypical of neurodermatitis.

Psorias--sometimes itches severely but it is the profuse guttate eruption and not the large and less numerous patches which itch most commonly; scales generally are larger and because of their enclosed air spaces have a brighter metallic luster; the large patches have rounded or polycyclic outlines and tend to clear centrally, producing circinate figures.

Lichen planus--more bluish color; individual papules are polygonal rather than rounded, are more commonly shiny, and display characteristic minute

transverse striations. Their tendency to linear arrangements along scratch marks also is pathognomonic.

Seborrheic dermatitis--rounded, polycyclic outlines of patches with yellowish greasy scale; most frequently involves sternal, interscapular, temporal, parietal and other sites not common to neurodermatitis.

Scleroderma--circumscribed patches, rarely itch, smooth surface with outline rounded or bandlike; color chiefly of bluish and reddish tints, and intensified skin markings and scaling are absent.

TREATMENT

Neurodermatitis is one of the most difficult and disappointing dermatologic disorders to treat. There is no specific cure although remissions are usually numerous and in most cases the disease abates in middle life or before. Treatment is aimed primarily at alleviating the pruritis.

Members of the neurogenic school can cite many remissions brought on by change in environment or dissipation of emotional tension. Members of the allergic school can boast cures brought on by desensitization or by removal of offending allergens. However, in the big majority of cases attempts to control neurogenic or allergic factors are ineffectual.

Among the neurogenic theorists, Stokes (15) urged a careful functional study of patients leading to their talking and "unloading". They must be made to understand their problem, reassured, readjusted, and given a new mental attitude. He claimed a technic of neuropsychiatric re-educating the patient to his environment was of great worth in displacing phenol, menthol and the barbiturates in providing relief. Becker (13) pointed out that therapeutic response to

rest, relaxation, sunshine, sedation and re-education as protection against worry and strain has been gratifying.

However, Wise (77) felt that therapy based on neurogenic lines was most applicable to well-to-do patients who could afford to indulge in such luxuries as consultants, hospital rooms, nurses, and plenty of time.

Members of the atopic school admit they haven't the answer to treatment although in some cases removal of offending allergens effects a cure. Hill and Sulzberger (35) pointed out that until there was better understanding of the mechanism which makes atopic sensitization possible the best method of treatment is symptomatic; however, this should include attempts to determine specific sensitivities and withdrawal of responsible allergens from the diet or environment.

Hill (34) suggested hyposensitization and named three ways to attempt as much: (a) by feeding gradually increasing amounts of the allergic food, (b) by intracutaneous or subcutaneous injections, (c) by peptone method of Urbach, in which before each offending food is eaten a specific peptone tablet is taken orally.

Meanwhile, experimenters have made many other attempts to unearth a successful treatment. Histaminase, calcium galactogluconate calcium bromide, hypoglycemic reactions, unsaturated fatty acids, thyroid extract, and elastic adhesive dressings have been tried.

As previously stated, Cumming and Laymon (61) and Smith and Hughes (62) found histaminase of little or no value. Neither has the use of thyroid extract proved effective. Tillim and Squires' trial with insulin shock also has been mentioned.

Reuter (78) recommended the use of calcium galactogluconate calcium bromide as an adjunct in the treatment of neurodermatitis. In a series of 20 cases he found it to be a satisfactory sedative in addition to providing the empiric benefit of calcium. He detected a definite lowering of the psychogenic and neurogenic effect of the disease was invariably accomplished and much of the self-induced trauma was avoided.

Taub and Zakon (79) tried purified linseed oil, an unsaturated fatty acid, in doses of 15 to 30 cubic centimeters three times daily, in eight patients. Their results were "universally poor", however.

Kulchar (80) reported elastic adhesive dressings of value in those lesions refractile to irradiation

and chemicals. He painted the involved area with five per cent gentian violet, allowed it to dry, and then applied a spiral bandage of elastic adhesive tape. This relieved the itching promptly. The bandage was removed and reapplied each week for three or four weeks until involution was complete.

Smith and Hughes (62) in 12 cases found no benefit from a high protein, low sodium and acid ash diet along with the administration of potassium chloride. In some cases they found hydrochloric acid, in doses up to 70 drops three times daily, of definite benefit.

Locally for the relief of itching, the usual antipruritic lotions, ointments, powders and wet dressings are recommended; the most popular ingredients include menthol, phenol, camphor, salicylic acid, resorcin, zinc oxide, calamine, crude coal tar paste, ichthyol, boric acid, potassium permanganate, ammoniated mercury, benzocaine, and so forth. Nearly every dermatologist has his own pet combinations although those employing menthol, camphor and phenol are perhaps the most popular. Incidentally, Stillians (81) suggested cresol in alcoholic dilution, beginning with 25 per cent, for lesions situated in the scalp.

As an example of treatment regimes, the recommen-

dations of Becker and Obermayer (52) are offered:

Dry type of neurodermatitis described by Becker--three per cent ichthyol-zinc paste or menthol-phenol paste at night with aquaphor lipoid cream during the day; avoid soap and water and cleanse areas with mineral oil; crude coal tar ointment may be used at night if there is no irritation. If the lesions are chronic, pine tar and salicylic acid in a 30 per cent zinc oxide ointment may be used, starting with .5 per cent of each and gradually increasing the strength of each up to five per cent.

Wet type of neurodermatitis described by Becker--the ichthyol-zinc paste or menthol-phenol paste if there is no inflammation; for inflammation, wet dressings followed by White's crude coal tar ointment.

Incidentally, other more or less unsuccessful attempts at therapy have included the use of arsenic internally, pilocarpine, ephedrine, atropine, strontium bromide, sodium and calcium thiosulfate, hyperpyrexia, turpentine and adrenal cortex extract.

However, if local applications fail to bring relief, most dermatologists depend on roentgen irradiation; weekly treatments, usually in the neighborhood of 75 roentgens, for several months are generally, but

not always, effective. The irradiated lesions may reoccur, however, and further treatment generally is without relief and is dangerous. Ultraviolet ray therapy in sub-erythema doses oftimes if alleviating, although there are some cases made worse.

But as in all dermatologic lesions, overtreatment must be avoided. Nearly all authors stress that topical applications and irradiation must not be too irritating because more times than not vigorous treatment may do more harm than good.

Comment

Treatment is not specific and generally not very effective. Psychotherapy and attempts to desensitize or remove offending allergens may help some cases but as a rule are unsatisfactory. Irradiation and anti-pruritic preparations give best relief.

VARIATIONS AND COMPLICATIONS OF NEURODERMATITIS

Keratoderma Climactericum

This is a condition, first described by Haxthausen (82) in 1934, which Becker and Obermayer (52) and Lynch (83) consider to be a special form of neurodermatitis. Haxthausen applied this term to a clinical picture of circumscribed hyperkeratosis of the palms and soles, occurring in women in association with the climacteric and accompanied by various general signs and symptoms, of which obesity and arterial hypertension were those most frequently encountered.

Brooke (84) in 1891 is believed to be the first to report this condition, describing a sharply circumscribed, dry, hard, thickened overgrowth of horny tissue in palms and soles of a woman, 54.

Haxthausen did not link the condition with neurodermatitis; he connected it with the menopause, obesity, hypertension, and arthritis of the knee. Lynch said that clinically keratoderma climactericum began with development of one or several slightly elevated dull red to red-brown sharply circumscribed round or oval papules. Lynch listed as salient features: scaling not prominent at first but becoming so as papules enlarged

and coalesced; variation in ultimate extent of eruption, the instep usually being spared; exaggeration of skin folds, oftimes bleeding fissures; thickening most prominent at the pressure bearing points.

Lynch, in reviewing ten cases, concluded plantar involvement more common than palmar and that itching and burning were likely to be present long before eczematization was evident. Histologically he noted a greater degree of inflammatory reaction than Haxthausen--also swelling of collagenous fibers and degeneration of the elastin. He detected extensive hyperkeratotic thickening of the stratum corneum without evidence of parakeratosis; papillae showed increased vascular supply, also an inflammatory reaction. In most of Lynch's cases, a favorable effect followed administration of diethylstilbesterol for as short a period of one or two weeks.

Lynch labeled keratoderma climactericum a form of neurodermatitis because there could not be pointed out clinical or microscopic features which allowed differentiation. However, he felt it should be considered in a different category because the eruption was associated with evidence of disturbed estrogenic activity.

Becker and Obermayer differed keratoderma

climactericum from ordinary palmar and plantar neurodermatitis by presence of rather hyperkeratotic lesions on the ends of the toes.

Smith (85) in 1942 reviewed 25 cases of lichen simplex chronicus and found all had evidence of the disease on sites other than the palms. Most patients were over 50 years--only three were under 40; one third had a personal allergy history; one third had a family allergy history; most told of related nervous strain. She found differentiation from keratoderma climactericum rather difficult since in both types of disorder the center of the palms and the pressure points of the soles were involved frequently. However, in keratoderma itching was typically absent and the blood pressure elevated, while in lichen simplex chronicus the blood pressure was normal and itching was a common complaint. As regards etiology, Smith noted low sugar tolerance and thought this might represent a state of functional exhaustion on the part of the endocrines.

By the way, Goldberg (86) reported in 1937 a typical case of keratoderma which responded to estrogens and irradiation.

Cataract

Cataract is a complication of neurodermatitis as

rare as it is mystifying; but only recently has it come to be considered a complication of neurodermatitis. Prior to 1900 there were numerous instances in the literature citing cases of cataract associated with skin lesions. Ollendorf and Levy (87) reviewed the literature in this respect, the first case report appearing in 1868; they found that most patients were older children and young adults.

Brunsting (37) also checked the literature on cataract and neurodermatitis. He wrote that in none of the reported cases has there been any evidence of a congenital disturbance and that the usual causes of presenile cataract were absent. Neither did he find any history of endocrine dysfunction in the sense of diabetes or thyroid or parathyroid insufficiency; nor was there any relationship with previous medication or irradiation in these cases. Brunsting offered a good description of these cataracts as follows:

The lenticular opacities are destructive, usually of insideous onset, although they may proceed from the initial to the late stages of maturation through the short period of three months. At first the opacities may give rise to no symptoms and may be appreciated only by examination of the lens by the slit lamp

microscope. The earliest changes appear as granular deposits in the inner surface of the anterior capsule or slightly behind the capsule within the cortex. A diffuse greyish translucency intensifies the slit lamp beam through the lens. As the opacification increases, the suture lines that make up the anterior and posterior "y" become prominent, giving a feather-like appearance, which becomes fainter and more fimbricated at the extremities. Granular deposits appear at the posterior pole and gradually extend peripherally. They appear dull gray in the direct light beam. As the cataract develops the lens takes on a diffuse grayish appearance, and the details which were obvious in the incipient stage are obliterated. A full mature cataract is silver gray or light cream and does not reflect a shadow of the iris. The lens capsule is fragile and easily ruptures at operation. The lens cortex is scanty and the nucleus is firm and a light amber tint. The cataract is not easily removed by linear extraction because of sclerosis of the nucleus.

Brunsting stated nothing is known in regard to the mechanism responsible for their production; however, he asserted the association between the cutaneous syndrome and the cataract was beyond the accident of mere happening.

Daniel (88) in 1935 reported three cases which she said not only fall into the group "opacification of the lens in young adults accompanied by skin manifestations", but also by virtue of the history and positive allergic reactions could justify the term "allergic cataracts". She mentioned that the eye was one of the sites were allergic responses occurred.

Meanwhile, case reports are becoming more numerous.

Sulzberger (89) in 1936 told of a male, 23, with a recurrent neurodermatitis who two and a half months following an acute flareup noted a blurring of vision in the right eye. Examination showed a posterior capsule opacity of the right lens and a similarly situated cataract beginning on the left.

Tosteven (90) in 1938 reported an anterior and subcapsular cataract in a young man with neurodermatitis. The same year Cazort and Cook (91) told of a girl, 15, who after eight years with neurodermatitis lost her vision in three months. McDannaold (92) in 1943 reported two cases in which surgical intervention gave good results, concluding the condition lent itself well to surgery.

Another possible eye complication of neurodermatitis

is keratoconus. Bereston and Baer (93) recorded two cases of keratoconus in neurodermatitis patients and speculated it might be a rare complication since they found only one similar case in the literature. They admitted it might be a coincidental finding but suggested it could be a hitherto unrecognized complication.

Incidentally, Gifford (94) described keratoconus (or conical cornea) as a corneal degeneration beginning about the tenth year of life, running a typical course of progression and then at a certain point becoming stationary. The cause he said was unknown.

Neuronychia (Onycholysis)

This condition is considered by Becker and Obermayer (52), and apparently by them alone, as a complication of the neurodermatoses because it is sometimes seen in company with these diseases or with signs of circulatory instability. Neuronychia, which term Becker prefers over onycholysis, starts at the distal end of the nail or at one corner. The nail becomes translucent and yellow in the involved portion and often starts to separate from the nail bed; this separation progresses until in extreme cases it extends as far back as the lunule. In wet neurodermatitis and dyshidrosis, Becker described another form of neuronychia in which there was superificial punctate

pitting of nails, irregular thickening or thinning and splitting of the nail bed; this leads to ridges and grooves transversely. Becker treated neuronychia with White's crude coal tar ointment beneath the nail, occasional irradiation, and the avoidance of soap and water; he described prognosis as to remission as good.

Fox (95), considered an authority on diseases of the nails, associated onycholysis with a disturbance of the endocrines. He reported a low basal metabolic rate in many of his cases, with thyroid medication usually producing improvement. Fox did not link the disorder with the neurodermatoses.

PROGNOSIS

As previously stated, neurodermatitis is a self-limited disease which usually abates spontaneously in middle age or before. The disease itself is never fatal. In no place in the literature was neurodermatitis mentioned as predisposing to malignancy.

CONCLUSIONS

All the pertinent literature on neurodermatitis, associated conditions and complications has been reviewed and summarized. Particular attention has been paid to etiology and treatment.

Chronic disseminated neurodermatitis is a well established clinical entity but so far no satisfactory explanation of its pathogenesis has been produced. Neurogenic and allergic theories are unproved and of little practical value in treatment.

Very intere ting mineral changes in skin lesions have been found and have revealed factual evidence on which may be built future investigations. Research into the role of the parathyroids and other endocrines may be enlightening.

At present the only treatment is symptomatic and this consists principally of irradiation and antipruritic preparations. The disease usually abates in middle life and apparently has no effect on longevity.

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