

## ACRODERMATITIS CHRONICA ATROPHICANS (PICK-HERXHEIMER)\*

## REPORT ON A SOUTH AFRICAN CASE AND A DISCUSSION OF THE RELATIONSHIP OF ACRODERMATITIS CHRONICA ATROPHICANS TO ERYTHEMA CHRONICUM MIGRANS AND LYMPHADENOSIS BENIGNA CUTIS

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Acrodermatitis chronica atrophicans (ACA) is relatively common in Central, Eastern and Northern Europe. Elsewhere it is rare and many of the cases reported from other lands have occurred in immigrants from the endemic areas.

In France the great majority of cases have been found in the north-east, where Pautrier, of Strasbourg, and his colleagues published numerous studies in the 1920s. This work is summarized in the *Nouvelle Pratique Dermatologique*,<sup>1</sup> where the historical background and a detailed description of the disease will be found. ACA is uncommon in Britain. I found only 3 cases reported in the *British Journal of Dermatology* during the years 1936 to 1956; two of the patients were German, the other Polish. According to Wallace,<sup>2</sup> of the patients with ACA seen at St. Thomas's Hospital, London, only one (a dubious case) was British-born. Prakken<sup>3</sup> states that ACA is rare in Holland and that he sees perhaps one case in a year.

Marchionini,<sup>4</sup> in a recent article, states that he never saw a case during the 10 years he practised in Turkey and that he found none reported in the Turkish literature. He quotes some American observers as maintaining that ACA is found in the USA only among immigrants from Central or Northern Europe. This is an overstatement; Montgomery and Sullivan<sup>5</sup> have reported a series of 45 cases of ACA, seen at the Mayo Clinic, in which 6 patients were native-born Americans, one a Mexican, 8 Scandinavians, and the rest from Europe or Russia. They also cite reports of ACA in natives of South America, Greece and Turkey.

## CLINICAL

ACA may begin at any age but the first signs appear oftenest during the 5th or 6th decades. In many reported series women have been affected much oftener than men; for instance in Montgomery and Sullivan's series<sup>5</sup> there were 37 women and 8 men, in Hauser's 182 women and 52 men<sup>6,7</sup>. The majority of cases occur in country-dwellers. Trauma, exposure to cold, or insect bites, have preceded the onset of the disease in some cases and familial incidence<sup>8</sup> has been reported on a few occasions.

The generally accepted name 'acrodermatitis' is not always appropriate because the actual extremities are sometimes spared, and 'dermatitis chronica atrophicans' or 'dermatitis atrophicans progressiva' (Jadassohn) are more apt.

Sites of election for the lesions are the limbs, especially the legs, and distribution is usually roughly symmetrical, but may be unilateral or confined to a limb. Although spread is often halted on the limbs, extension to the buttocks or breasts is not uncommon and nearly the whole body surface may sometimes be affected. An early, inflammatory phase is followed by one of atrophy and it is in this latter phase that patients are usually first seen. Progress is nearly always extremely slow over many years but rapid evolution

over a few months has been reported in a few cases.

The primary, inflammatory lesions (solitary or multiple) appear, in most cases, as ill-defined reddish-violet patches, non-infiltrated and fading on pressure, on the dorsa of the hands or feet or on the legs or arms, especially over bony prominences. Rarely, the primary lesions are little yellow or red dermal papules or nodules. The erythematous areas develop a soft, diffuse or nodular infiltration and slowly spread peripherally; their borders become better defined and rounded or serpiginous as the patches merge. Symptoms are generally unimportant but there may be a little itch or hyperaesthesia in the affected skin and the underlying bones may be tender to pressure and the joints stiff. At this stage the appearances may suggest erysipeloid, erythema chronicum migrans or, possibly, some vascular disorder.

Activity persists for years in the advancing edges but in the central areas the infiltration disappears partially or entirely and the skin becomes thin and atrophic. The chief characteristics of ACA in the established phase are cutaneous atrophy, variegated erythema and visibility of the superficial veins. Atrophy of the skin is general in the affected areas but is most obvious over the knees, elbows and buttocks. The skin becomes papery or collodion-like, dry, easily eroded, practically hairless, and so inelastic that it seems too big and loose for the areas it covers. It is erythematous in varying shades from pink through red and violet to purple. Superficial veins stand out clear and blue through the transparent skin and the tendons and muscle masses are sharply outlined.

Infiltration persists in the active edges and may be found in patches under the atrophic skin elsewhere, particularly about the knees and elbows. Fibrous dermal nodules are often found over the extensor surfaces of the joints. Sclerodermiform infiltration and fibrosis sometimes occurs, almost always on the limbs, with the formation of finger-width ulnar or tibial bands or a gaiter-like sclerosis around the lower third of the leg. Macular or striate atrophic lesions, patches of poikiloderma, pigmentary changes, varicosities, leg ulcers and osteo-arthritis may be found with ACA and squamous carcinoma and sarcoma have been reported to develop in the lesions. Degos<sup>9</sup> mentions the occasional association of visceral cancer with ACA.

The general health is little affected and no major visceral changes are found. In a series of 234 cases Hauser<sup>6,7</sup> found lymphadenitis (sinus catarrh and plasmocyte reaction) in 36, and enlargement of the liver in 6, and of the spleen in one. The erythrocyte sedimentation rate is often increased and hyperglobulinaemia may be found but there are no constant or characteristic changes in the blood. There may be proliferation of plasmocytes in the bone-marrow.

The clinical picture in the late phase is so striking that the diagnosis is in most cases at once obvious. In rare cases where confusion with scleroderma, poikiloderma or senile atrophy might arise, the problem is usually solved

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Fig. 1. Acrodermatitis chronica atrophicans. Fig. 2. Acrodermatitis chronica atrophicans. Fig. 3. Acrodermatitis chronica atrophicans.



by histological examination. There are, however, rare cases such as those recently described by Degos *et al.*<sup>10</sup> and by Nonclercq<sup>11</sup> in which ACA has seemed to develop from apparently typical lesions of scleroderma.

The histological changes in ACA<sup>9,12-14</sup> are reasonably characteristic. In the early, inflammatory phase the epidermis is thinned and flattened, with a normal or hyperkeratotic stratum corneum; the interpapillary processes are effaced. Immediately under the epidermis is a narrow band of dense collagen with rare cellular elements and no blood vessels. Under this is a well-defined, broad band of cellular infiltrate below which small patches of infiltration are seen in perivascular distribution. The cells composing the infiltrate are lymphocytes, histiocytes, plasmocytes, fibroblasts and, sometimes, mast cells. Lymphocytes or plasmocytes predominate in most cases. There is interstitial oedema of the dermis and the collagen fibres show hyaline degeneration. The dermal blood vessels are telangiectatic, their walls are swollen, and thromboses may be seen. The elastic fibres are degenerate and fragmented.

In the atrophic stage degenerative changes are evident at all levels and in all components of the skin except the blood vessels, which remain dilated. The epidermis is reduced to a few layers of cells and its border with the dermis is quite straight. The changes in the collagen and elastic tissue persist or are accentuated, but the infiltrate remains only as discrete, narrow, horizontal bands between the collagen fibres. Hair follicles and sebaceous glands disappear but some arrectores pilorum and sweat glands usually survive. In nodules and sclerodermiform bands and plaques the epidermis is thinned and hyperkeratotic and the dermis is at first infiltrated, later fibrotic.

I have seen only two cases of ACA during 9 years in South Africa, one in a middle-aged German woman who had developed the disease in Germany and in whom all evidence of activity in the atrophic lesions had disappeared, and a second, presented here, in a South African woman who had never been overseas. Loewenthal,<sup>15</sup> of Johannesburg, has also seen a case in a South African farmer from the Cape Province.

#### CASE REPORT

The patient was a White woman, age 79 years, who was admitted to Prof. J. N. de Villiers' wards at the Karl Bremer Hospital, Bellville, for gynaecological investigation. She was found to have an extensively invasive, grade 4, squamous carcinoma of the cervix uteri and a widespread dermatosis. Only a vague history was elicited but it appeared that the skin lesions had first appeared on the limbs some years before and had slowly spread to involve the trunk and scalp. Symptoms were apparently negligible but excoriations on the scalp suggested that this area itched.

The skin of the dorsa of the feet, legs and thighs was extensively involved and lesions continued over the buttocks and back to the level of the tips of the scapulae. Anteriorly the lesions stopped abruptly on the thighs, spared the groins and reappeared on the abdomen and breasts. On the arms the elbow regions were most affected and the axillae and shoulders were normal. The whole scalp and a bordering band across the forehead were involved (Figs. 1, 2 and 3). No mucosal changes were found.

In the affected areas the skin was thin, dry, papery and atrophic; atrophy was most marked on the extensor surfaces of the knees and elbows and on the thighs and buttocks. Superficial scaling was obvious on the shins and a few shallow erosions (1-3 cm.) were seen on the backs of the thighs and buttocks. The colour of the skin was parchment-white relieved by erythematous patches, up to 10 cm. in diameter, ranging in shade from pink to purplish-red, and scattered areas of light brown pigmentation. Infiltration was absent except under some of the erythematous patches near

the margins, and even here it was of negligible degree. The scalp was atrophic and pink, with numerous small excoriations, and there were an obvious, though minor, general thinning of the hair. The transition from affected to normal skin was sharp and spread appeared entirely to have halted.

No fibrous nodules, sclerodermiform bands or scleroses were present, but there were many tiny milia scattered in that part of the skin which showed most atrophic changes. The superficial veins were not visible.

The patient was treated with terramycin for secondary infection of the genito-urinary tract during the fortnight she was in hospital, but this had no effect on the skin lesions, which were obviously in the terminal, atrophic stage.

#### Histopathology

A biopsy specimen of the skin was excised from an erythematous, slightly infiltrated patch on the anterior surface of the right thigh. The changes found were consistent with a diagnosis of



Fig. 4. Acrodermatitis chronica atrophicans. Hyperkeratosis and atrophy of epidermis. Infiltrate and telangiectatic blood vessels in oedematous dermis.

ACA in the atrophic stage. The stratum corneum was hyperkeratotic, but the epidermis as a whole was thinned and, in places, narrowed down to 3-4 cells in thickness; the stratum granulosum was present in patches. The demarcation between epidermis and dermis was rectilinear. Two milia were present (Figs. 4 and 5). The collagen fibres stained poorly and were distorted and separated by oedema. There was a diffuse cellular infiltrate throughout the dermis, most marked in the upper level and reaching to the dermo-epidermal junction, scattered and perivascular in the lower dermis, but not invading the hypoderm, which was normal in appearance. The infiltrate consisted mainly of lymphocytes and histiocytes, but many plasma cells and some fibroblasts were also present. No hair follicles were seen, but sweat glands, arrectores pilorum and some remnants of sebaceous glands were visible. The blood vessels were telangiectatic, with cellular infiltration of their walls and the surrounding tissue; no thromboses were found. The elastic tissue was grossly abnormal and reduced to small, often swollen fragments in disorderly arrangement (Fig. 6).

#### DISCUSSION

A great many theories about the cause of ACA have been advanced in the past and it has been suggested that it might

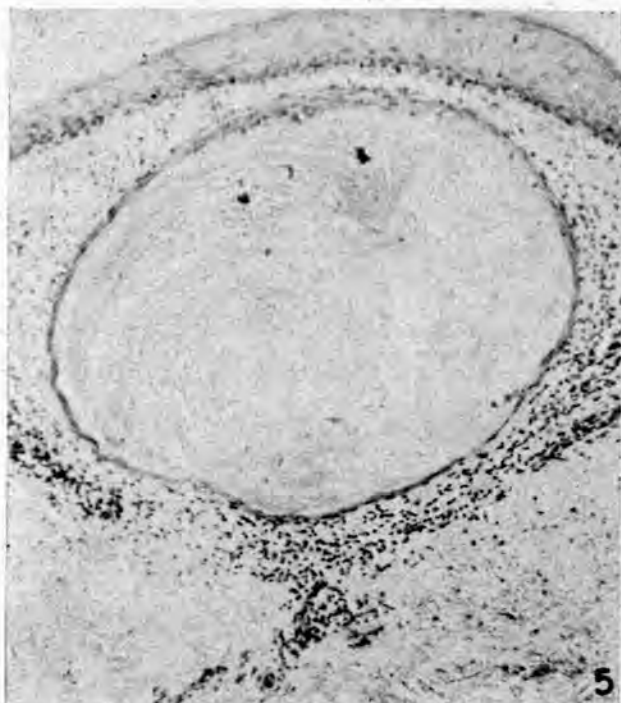


Fig. 5. Acrodermatitis chronica atrophicans. Milium cyst.

be due to endocrine or sympathetic disturbances, to leprosy, syphilis, tuberculosis or some unspecified micro-organism, or to vascular abnormalities, and so forth.

The field of speculation was narrowed by the discovery that ACA can be cured in the early stages or arrested, atrophy remaining, at any stage by treatment with penicillin or other antibiotics such as aureomycin, terramycin, streptomycin and erythromycin. Even after the advent of penicillin some authors continued to resist the idea that ACA might



Fig. 6. Acrodermatitis chronica atrophicans. Elastorrhexis.

be caused by an infective agent and suggested that the penicillin acted not as an antibiotic, but by virtue of some mysterious effect on the vegetative nervous system. The demonstration by Götz<sup>16,17</sup> that the early lesions can be reproduced in humans by the subcutaneous implantation of fragments of skin from patients suffering from ACA has convinced most observers that the disease is, indeed, infectious. From the presence of plasma-cell infiltrates and vascular changes it was argued that ACA might be a spirochaetosis, but no confirmation of this theory is forthcoming from bacteriological or serological studies. The balance of opinion is at present in favour of a virus as cause, but this theory is equally unconfirmed.

It has already been noted that a history of insect bites preceding the appearance of the lesions may be given by patients with ACA. The frequency with which the primary lesions appear on the limbs, especially the legs, and the predominance of women (limbs exposed) over men and of country-dwellers over city-dwellers are points suggesting that ACA may be spread by an insect vector. German observers (cited by Brumpt<sup>18</sup>) have suggested that ACA may be inoculated by the bite of *Ixodes ricinus*, and Hauser<sup>8</sup> notes that the geographical area of distribution of the disease coincides closely with that in which this tick is found.

Patients with ACA have occasionally been found also to bear lesions of erythema chronicum migrans (Afzelius-Lipschütz) (ECM) or of lymphadenosis benigna cutis (Bärf-verstedt) (benign lymphocytoma of skin) (LBC); and ECM and LBC have been found together (literature reviewed by Paschoud<sup>19</sup>). Both ECM and LBC have recently been successfully transmitted in experiments on humans and their relationship to ACA is of considerable interest.

#### ERYTHEMA CHRONICUM MIGRANS

The resemblance of the early lesions of ACA to those of ECM has already been mentioned and this resemblance is again seen in the lesions produced in Götz's experimental cases of ACA<sup>16,17</sup>. The primary lesion of ECM is a red, infiltrated papule or little plaque. Peripheral spread and central healing, without atrophy, produces a continuous or broken ring with a dusky-red infiltrated border 5-20 mm. in width. Very large areas can be included within the advancing edge, but eventually, after a few months to a year, the disease heals and leaves no trace. A solitary lesion is the rule and there are never more than a few. Sites of election are the legs, but any area may be affected. The general health is usually unaffected, but febrile forms occur and cases with monocytic or leucocytic meningeal reactions, radiculitis and even encephalitis have been reported. Treatment with penicillin and other antibiotics is rapidly curative in both simple and complicated cases. The histological picture is non-specific, with a dermal infiltrate consisting largely of lymphocytes and occasional eosinophils. Successful experiments in passage of ECM are reported by Binder *et al.*<sup>20</sup>

In many cases of ECM there is a history of an insect bite preceding the appearance of the lesion, or evidence of such a bite may still be obvious. According to Brumpt<sup>18</sup>, the insect responsible has always been *Ixodes ricinus* in those cases which were carefully investigated. No special mention is made of the geographical distribution of ECM in the standard works on dermatology but it is noteworthy that most of the literature on the disease has emanated from those countries where ACA is common. Case reports in the British literature are few and the editors of the *Year Book of Dermatology* remark on the rarity of ECM in the USA.<sup>21</sup> I have never seen a case in South Africa, but Jacobson,<sup>22</sup> of Cape Town, has seen one.

#### LYMPHADENOSIS BENIGNA CUTIS

The condition with which we are here concerned is the localized variety of LBC, in which lesions, solitary or grouped, are found



oftenest on the face, neck and ear lobes, less frequently on the chest, trunk, genitals and elsewhere. The lesions are dusky or brownish-red infiltrated papules, nodules, plaques or rings 1-5 c.m. in diameter. Widely spreading or atrophic lesions are not described. The histological picture in early lesions is of a dense, diffuse lymphoreticular dermal infiltrate with an admixture of plasma cells and eosinophils. In older lesions lymphoid follicles give an appearance similar to that seen in a lymph gland. Neither visceral lesions nor blood or marrow changes occur and the condition is unrelated to the lymphomas.

LBC tends in many cases to spontaneous cure after some months to a year or more, but very chronic cases also occur. Penicillin sometimes, but not invariably, causes temporary improvement in, or disappearance of, the lesions and resolution of older lesions is sometimes hastened by X-ray therapy. It is interesting to note that Bianchi<sup>22</sup> used penicillin to treat LBC because of its histological resemblance to ACA, in which penicillin is curative. Paschoud<sup>19</sup> has recently succeeded in reproducing the lesions of localized LBC in human passage experiments. A history of insect bites preceding the onset of lesions is sometimes given.

From the literature it would appear that where ACA and ECM are found, so too is LBC; but the geographical distribution of LBC is by no means so confined as that of the other two diseases. LBC is of world-wide distribution. Cases are fairly frequently reported in the British and American literature. I have seen 3 cases in South Africa and know of a few others.

The status of LBC in its localized and disseminate forms is far from clear, and there is no doubt that the cases described under this title are not all identical. Some, judging from the outcome, were malignant lymphomas, and others would appear to have been cases of lymphocytic infiltration of the skin (Jessner). Reaction to insect bites may persist for a year or two and present histological appearances identical with those seen in LBC<sup>24</sup>.

A diagnosis of LBC is not one which should lightly be made. There are no clinical or histological features which distinguish the condition with certainty from the malignant lymphomas or reticulo-granulomas and these latter conditions may sometimes long remain apparently localized in the skin before visceral lesions are detectable.

The fact that localized LBC can be reproduced in man by inoculation experiments suggests, but does not necessarily imply, that an infective factor may be involved. It must be remembered that some mesodermal tumours of animals are capable of passage. If some or all cases of localized LBC are identical with chronic insect-bite reactions there exists the possibility that some toxic substance persisting in the lesions accounted for the success of Paschoud's experiments.

#### CONCLUSIONS

It seems probable that the occasional findings of lesions of ACA and ECM or LBC occurring on the same patient are not fortuitous but signify that the diseases are directly or indirectly related.

ACA and ECM are most commonly found in the same geographical distribution. The early lesions of ACA resemble clinically those of ECM and appear on the same sites of election. Both diseases are rapidly controlled by the antibiotics and both have been experimentally reproduced in man. There are grounds for suggesting that ACA and ECM have a common, microbic cause and that ECM may be an abortive form of ACA.

The lesions of LBC may clinically resemble those of early ACA or ECM but the subsequent development of the latter diseases makes them easily distinguishable. All three diseases present the histological picture of a chronic granulomatous process in the early stages, but the follicular structures seen in the fully developed lesions of LBC are not reproduced in the other two diseases. Where ACA and ECM are oftenest encountered, so too is LBC, but it is by no means so rare as the former in other lands. Whereas there is convincing evidence that ACA and ECM are infectious diseases, this is not so with LBC. It is probable that

a particular tick, *Ixodes ricinus*, is commonly involved in the spread of ACA and LBC. Although insect bites may play a part in the cause of some cases of localized LBC it seems improbable that ticks could frequently be incriminated; the region of the face, site of election for localized LBC, is not one where tick bites are often seen. It seems unlikely that LBC is so closely related to ACA and ECM as these diseases are to each other. The form of LBC sometimes found in cases of ACA and ECM may well be simply a chronic lymphoid reaction to the bite of the insect vector of the latter diseases.

There seems little doubt that an insect vector is often if not always involved in the spread of ECM and this is probably also the case in ACA, though the evidence is obviously not so striking in a disease that is often diagnosed only months or years after the onset of symptoms. The insect suspected of transmitting these diseases is *Ixodes ricinus*, a species of tick with a holarctic distribution, common in Europe and extending far into the palearctic part of Asia. This tick is known to transmit *Piroplasma bovis*, the cause of haemoglobinuria of cattle, and the viruses causing louping ill, tick-borne fever and the tick meningo-encephalitis of Russia. It can transmit Rocky Mountain spotted fever under experimental conditions and has been reported to cause pyaemia in sheep in England and tick paralysis of sheep in Crete.<sup>18</sup>

Hauser<sup>6</sup> has stated that the geographical area in which ACA is commonest corresponds closely to that in which *Ixodes ricinus* is found. It would be more accurate to say that ACA is commonest within the area inhabited by the tick, since there are vast areas, including Britain, most of France, Southern Europe and North Africa, where ACA rarely occurs spontaneously but where *Ixodes ricinus* is found and may transmit other diseases. This does not imply that *Ixodes ricinus* is not a vector of ACA, but it suggests that some other factor, possibly climatic, may also govern the transmissibility of the disease.

In favour of the concept that *Ixodes ricinus* is the common vector of ACA is the fact that ACA is uncommon in native-born Americans in spite of the fact that the USA has in the last century received millions of immigrants, and presumably many infected persons, from the endemic areas of Europe. Nuttall *et al.*<sup>25</sup> stated that *Ixodes ricinus* was found in the USA, but it is now thought that, though it may occur, most records apply, in fact, to other closely related species such as *Ixodes scapularis* or *Ixodes cookei*.<sup>26</sup>

*Ixodes ricinus* is not found in South Africa, but among the many ticks found here are two Ixodids, *Ixodes rubicundus*, the Karroo paralysis tick, and *Ixodes pilosus*, the Sourveld tick, whose distribution has been plotted by Theiler.<sup>27</sup>

The occurrence of spontaneous cases of ACA and ECM outside the area of distribution of *Ixodes ricinus* makes it plain that the intervention of this tick is not essential for the spread of these diseases. Some other species of tick or even an entirely different type of biting or stinging insect may occasionally intervene, or it could be postulated that direct contact with an infected person might, in certain circumstances, allow passage of the causative organism.

#### SUMMARY

A case of acrodermatitis chronica atrophicans in a South African woman is described and the literature on the con-

dition is briefly reviewed. Some speculations are made on the relationship between acrodermatitis chronica atrophicans, erythema chronicum migrans and lymphadenosis benigna cutis.

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