The skin manifestations associated with leukaemia and allied conditions / Sir Humphry Rolleston, Bt., K.C.B., M.D., D. Sc., P.R.C.P.

THE SKIN MANIFESTATIONS ASSOCIATED WITH LEUKÆMIA AND ALLIED CONDITIONS.*†

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INTRODUCTION.

A DISCUSSION of this kind is of special value, as it deals with a subject on the borderland between general medicine and dermatology, and thus tends to bring together for their mutual benefit those whose devotion to their own line of work might otherwise isolate. In the first place it is advisable to mention the conditions allied to leukæmia that come within the scope of this discussion. Some of the conditions described as causing cutaneous manifestations may be neglected because they are probably more accurately included under other headings. As lymphodermia perniciosa was described by Kaposi in 1885, before differential blood-counts were in vogue, it cannot now be regarded as a distinct condition or decided whether it was leukæmia, or, as some consider, mycosis fungoides. It is therefore desirable that the term "lymphodermia perniciosa" should be allowed to lapse. "Pseudo-leukæmia," a term responsible for much confusion, will be omitted, as it is probably covered by the aleukæmic phase of leukæmia or by Hodgkin's disease.

C. Sternberg's leukosarcoma is characterized by a tumour, in the vast majority of cases in the mediastinum, glandular enlargement, infiltration of the viscera, and eventually by the escape into the blood of the tumour-cells, which are usually large lymphocytes, 5–6 μ in diameter.

Chloroma, though considered as distinct from, evidently is allied to

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Sternberg's leukosarcoma; Weber and Wolf indeed remark that cases of leukosarcomatosis other than chloroma may be regarded as chloro-sarcomatosis without the green pigment which characterizes chloroma. Both these conditions, as well as leukæmic growths in the skin, might be included under the umbrella-like term of nodular leukæmia (Gordon Ward), if no attention be attached to the chronological relations of the tumours and the blood change, the tumour formation preceding the blood change in leukosarcoma, and following it in chloroma and leukæmia, though the occasional occurrence of a reversed sequence must be admitted.

Myeloid leukæmia and erythræmia (polycythæmia rubra, Vaquez-Osler disease) are closely related, both being manifestations of exaggerated, and possibly neoplastic, activity of the bone-marrow. Erythræmia may be followed by myeloid leukæmia, and patients with myeloid leukæmia may become erythræmic. This subject has been recently discussed by Minot and Buckman. But as cyanosis and sometimes slight pigmentation appear to be the only cutaneous manifestations of erythræmia, no further remarks about this condition are necessary.

In considering the subject of leukæmia and allied conditions, time will not allow a discussion of the relation of leukæmia to lymphadenoma and other conditions in which the blood does not show any specific change, or to enter into the question whether the various conditions are phases of one fundamental process, the differences depending on whether or not the proliferating cells remain *in sitû* or pass freely into the blood. For even if they are stages in a similar or allied process, it is the cutaneous manifestations in these individual phases that claim our attention. As evidence of the difficult problems concerned, it will be enough to mention that lymphosarcoma, lymphoid leukæmia, and leukosarcoma have been grouped together as different manifestations of the same disease characterized by proliferation of the mononuclear cells of the leucocyte type, and have been separated from lymphadenoma, which is a distinct condition showing proliferation of the reticulo-endothelial system (Webster). Recently Douglas Symmers argued that lymphadenoma and chronic myeloid leukæmia are fundamentally related, probably representing different quantitative responses to the same type of provocative agent. Mycosis fungoides has been regarded as intimately related to chronic lymphoid leukæmia (Pardee and Zeit; Hazen), and on the other hand as the cutaneous form of lymphadenoma (Ranvier; Ziegler). The great

difficulty is how to label cases with cutaneous nodules histologically composed of lymphocytes, but without leukæmic blood changes.

The aleukæmic phase.—In drawing a distinction between leukæmia and the allied conditions, difficulty arises from the occurrence in leukæmia of phases in which the blood is aleukæmic. It is therefore important to understand what is implied by the term aleukæmic phase of leukæmia, for it has been used in two senses. Some writers appear to mean that the blood is absolutely normal; others that, while there is no increase in the number of white cells, a differential count still shows the characteristics of leukæmia—a qualitative, but not a quantitative change. The second meaning, namely leukæmia without leucocytosis, is the correct one, for surely there is no reason to insist that normal blood is not leukæmic, whereas the blood with the qualitative but not quantitative characters of leukæmia stands in need of some special adjective. It has been suggested that such cases should be called "aleucocythæmic leukæmia," as the word "leucocythæmia" might be thought to imply leucocytosis, while leukæmia refers to the structural change in the cells (King, J. T.).

It is obvious that skin manifestations due to treatment of the primary disease by arsenic (pigmentation, keratosis, papillomas, herpes), benzol (erythema, purpura), X-rays or radium (pigmentation, burns) or subcutaneous or intramuscular injections (tumours) will not be considered.

Cutaneous tumours in leukæmia and allied conditions, though a matter of common knowledge, are so comparatively rare in practice that the question naturally arises why in certain cases the skin is picked out. Much the same problems are involved as in the incidence of cutaneous metastases in ordinary malignant disease. What is it that in certain cases of leukæmia and the allied conditions renders the skin an especially favourable site? Is it a question of previous damage or of senility of the skin so that it is unable to resist the process of infiltration, or is the skin in some way sensitized or exerts a chemiotactic attraction so that it favours the multiplication of cells reaching it by the blood-stream?

As bearing on this subject reference may perhaps be made to a case kindly communicated to me by Dr. J. H. Drysdale: a man with chronic lymphoid leukæmia, who, after two exposures to X-ray, each of them followed by a rigor, developed in a few hours a wide-spread papular eruption somewhat resembling measles. Examination of the blood showed auto-agglutination of the white cells, and thus suggested that extensive embolisms of the cutaneous vessels had

occurred. The rash gradually faded, but biopsical examination showed lymphocytic infiltration of the skin. It is conceivable that similar auto-agglutination of the white cells may occur as the result of intercurrent infection and so initiate the cutaneous infiltration.

The skin manifestations associated with leukæmia and allied conditions fall into two obviously different groups—(1) infiltrations or tumours of the skin histologically identical with the primary disease, (2) various non-specific disorders and changes in the skin (dermatoses) such as perspiration, pruritus, pigmentation, prurigo, erythematous, desquamative, vesicular, bullous eruptions, due to toxins, possibly derived from cell destruction in the hæmopoietic system. These eruptions have been called leucemides by Audry; but the exfoliative erythrodermias are generally not included among the leucemides, though Boudet groups all the cutaneous manifestations of acute leukæmia, with the exception of hæmorrhages and growths, under that heading.

It might therefore be logical to take each disease, such as acute and chronic leukæmia, chloroma, multiple myeloma, lymphadenoma, and mycosis fungoides, separately, and to consider under each the skin manifestations due (*a*) to structural invasion of the skin by the disease, (*b*) manifestations due to poisons manufactured by, or in association with, the morbid process and conveyed to the skin, such as pruritus and rashes, and (*c*) changes in the skin secondary to pruritus. This plan will be followed with some modifications necessitated by comparative brevity.

Leukæmia.

With regard to leukæmia as a whole, it may be mentioned that two features stand out:

(i) Pruritus is remarkably rare as compared with what occurs in lymphadenoma; this perhaps may be correlated with the view that leukæmia is a new growth of the hæmopoietic tissues, whereas lymphadenoma is an infective granuloma. It should be mentioned, however, that Ellermann, from his investigations into leukæmia in fowls, opposes the neoplastic in favour of the infective nature of leukæmia in man. Leukæmia is widely stated to be accompanied by pruritus, but I have never seen this association, and have been able to collect only twelve recorded examples, and of these it is noteworthy that six are Ketron and Gay's (16) collected cases of universal leukæmia of the skin. This association with wide-spread infiltration of the skin suggests that a

mechanical factor may in certain circumstances be of importance, though it does not occur in neurofibromatosis or in multiple malignant metastases in the skin.

(ii) That chronic myeloid leukæmia is very rarely accompanied by cutaneous manifestations of any kind, thus contrasting with the rarer disease chronic lymphoid leukæmia, in which a considerable number of cases with cutaneous changes are on record. This difference is compatible with the belief that the two diseases are much further apart in their nature and ætiology than is generally believed. It might perhaps be imagined that toxins derived from lymphoid elements are more prone to irritate the skin than are the disintegrated proteins derived from destruction of the marrow-cells. This suggestion might be thought to be negatived by the absence of rashes in infectious mononucleosis (Sprunt and Evans), which is probably the same as glandular fever, and by the occurrence of cutaneous manifestations in a certain number of cases of acute leukæmia, which is often an acute myeloid leukæmia; but it must be remembered that acute leukæmia is prone to blood infections, which may thus account for a certain number of cutaneous manifestations.

The question has naturally been debated whether leukæmia cutis is a passive infiltration of the skin or an active proliferation—in fact a new growth as in chloroma. In chronic lymphoid leukæmia mitoses have been described in the skin lesions by Arndt and by Butler, but more recently Ketron and Gay (16) were unable to confirm this.

Leukæmia cutis or genuine leukæmic tumours of the skin, first described by Biesiadecki in 1876, may for convenience be considered as a whole, so as to avoid repetition under the headings of "acute" and "chronic." Cutaneous leukæmic tumours are very persistent, and seldom, as in Ketron and Gay's case (17), come and go. They usually grow slowly and do not ulcerate spontaneously, though, in rare instances, ulceration is due to trauma and sepsis. They may appear at any time in the course of the diseased; in some instances the cutaneous tumours precede the blood changes (Butler; Ketron and Gay (17)), thus clinically resembling the supposed transformation of lymphadenoma into leukæmia. Usually symmetrical, they most often occur on the face, scalp, cheeks and eyelids. The leonine aspect of the face may then resemble that of tubercular leprosy. The tumours are nodular, or flat, discrete, or may become confluent. They are usually slaty blue or plum-coloured, and may suggest a diagnosis of melanotic metastases.

Acute Leukæmia.

It is difficult to draw a hard and fast line between acute leukæmia on the one hand, and subacute cases and latent cases with acute terminal phenomena on the other hand; but a duration of symptoms for not more than three months may perhaps be taken as satisfactory for a diagnosis of the acute form. Acute leukæmia is now generally regarded as usually myeloid rather than lymphoid in character, and due to changes in the bone-marrow, the cells which pass into the blood being myeloblasts rather than lymphocytes or myelocytes. In the late stages the exhaustion of the bone-marrow may lead to a leucopenia, so that the condition is described as showing an aleukæmic phase (*vide* Sequeira and Panton). No attempt will be made here to differentiate the cutaneous manifestations of acute leukæmia into those associated with acute myeloid and those with acute lymphoid leukæmia.

The cutaneous lesions in acute leukæmia fall into the distinct groups of (i) definite leukæmic tumours, and (ii) various other changes, sometimes spoken of as dermatoses.

(i) The cutaneous tumours formed of leukæmic cells resembling those in the blood are much the same in appearance, namely, plum-coloured, nodular, discoid, or flattened, as those seen in chronic leukæmia; usually they are quite small, and, though they may be extremely numerous, rarely become confluent, as may occur in chronic leukæmia. In some cases, for example, that reported by Shaw and Loughlin, the total white count was not increased, though the differential count supported the diagnosis of an aleukæmic phase of acute lymphoid leukæmia. This contrasts with H. W. Barber's case of acute lymphoid leukæmia, slaty blue, plum-coloured nodules appearing first on the scalp, where one ulcerated, and later on the body, with a total white count of 400,000. Cases of multiple cutaneous tumours with the histological structure of leukæmic nodules, but without any characteristic blood changes, such as Lavenson's case of "acute leucopenic lymphatic leukæmia," cannot be regarded as leukæmia.

(ii) Cutaneous rashes are commoner in acute than in chronic leukæmia, and they are polymorphic, thus suggesting that their exciting cause is not necessarily always the same. Acute leukæmia has many of the features of an acute infection, but it differs from any one of the acute exanthems, such as scarlet fever, in the various forms of skin eruptions

that may occur. The most characteristic and the most frequent is purpura, which may indeed be considered to be almost part of the disease —a statement not applicable to the other cutaneous phenomena. It is probably caused by thrombosis or leucocytic blocking of the small vessels, but possibly it is sometimes the result of secondary infection and due to bacterial emboli. The hæmorrhages may be minute and petechial, or large, and the latter have been regarded erroneously as scorbutic. Hæmatomas are easily produced by slight damage (Boudet).

Herpes labialis is not uncommon at the onset of acute symptoms, and may be explained on the view that the suddenly diminished resistance allows the latent virus of epidemic encephalitis to become active to the extent of producing febrile herpes.

Acute and subacute exfoliative erythrodermias may appear (Porta).

The other rashes, which are grouped together by Boudet as leucemides, include papules or vesicles, hæmorrhagic bullæ (Schultze), a morbilliform exudative erythema (Poynton and McNee).

I have not met with the pruritus described in some instances among the cutaneous manifestations of acute leukæmia.

Chronic Leukæmia.

Chronic myeloid leukæmia.—In the terminal stages hæmorrhages may occur into the skin, but this probably depends on an acute phase with myeloblasts in the circulation—in other words to the supervention of acute myeloblastic leukæmia. But in rare instances hæmorrhages occur in the chronic stage.

In 2 out of 47 cases analysed by Vogel, multiple evanescent tumours apparently due to hæmorrhages deep in the subcutaneous tissues were noted. I have recently had under my care at the Victoria Hospital for Children, Chelsea, a girl, aged 14 years, with chronic myeloid leukæmia, who had transient subcutaneous tumours on the lower limbs; one of them followed a blow and showed distinct bruising around it, thus suggesting a similar origin for the others.

Jaundice is very rare in chronic myeloid leukæmia; Tixier and Troisier reported such a case complicated by hæmolytic jaundice, so that there was a combined lesion of the erythroblastic and leucoblastic tissues; they could not find a reference to this combination.

As already mentioned, leukæmic tumours or infiltration of the skin are very rare. In 1911 Hazen collected 5 cases, and since then I have

references to 3 cases (Saphier and Seyderheim; French; Ketron and Gay). Of these 8 cases, pruritus was reported in 2 (Nékam; Ketron and Gay). The head and neck may escape, as in the case W. Fox and I published, in which the lower part of the trunk was thickly covered with nodules, the larger ones being not unlike in shape, size, and colour, half a damson.

Chronic Lymphoid Leukæmia.

Chronic lymphoid leukæmia provides most of the examples of true leukæmic tumours of the skin. The tumours may be large, and on the face, which is the site of election, may produce a leonine appearance, resembling that in leprosy; they are usually of a livid red colour. The tumours may become confluent, but more often they are discrete, small or miliary; they may be so numerous as to be universal, and of this form Ketron and Gay have collected 5 examples (Arndt; Bernhardt, who quotes three others recorded by Riehl, Linser, and Rodler-Zykin), in addition to their own case, but did not include Butler's case. Ketron and Gay's six patients, whose average age was 55, all had pruritus. The resulting scratching may give rise to pruriginous papules. These leukæmic tumours may exist for some years (Bernhardt).

The total leucocyte count may be very high or it may be low, and in the latter event a differential count will justify the diagnosis of lymphoid leukæmia. But cases in which the blood does not show at any time the changes characteristic of leukæmia, even though the viscera present the histological characters of lymphoid infiltration, as in the cases published by Blankenhorn and Goldblatt and by Sweiter, should not be labelled leukæmic. This separation of cases which, except for the blood changes, are identical clinically and morphologically, is not in accord with some recent opinions, especially that of Arndt. Against this rigid criterion of the state of the blood in deciding whether or not the cutaneous change should be called leukæmic, is our knowledge that the blood may at first be normal and then become leukæmic. But to my mind it is right to designate a lesion as leukæmic only when the blood, whether quantitatively or qualitatively, justifies such a diagnosis.

The other skin manifestations in chronic lymphoid leukæmia are numerous and polymorphic; erythrodermia or general exfoliative dermatitis with more or less infiltration, which is generally separated

from the others called by Audry leucemides, is a difficult subject, and has given rise to some discussion.

Audry and Nanta put forward the contention that Hebra's pityriasis rubra is really nothing more than an extremely malignant leukæmic erythrodermia, but the blood-count of the case given in their article is far from convincing evidence in favour of this conclusion. It might be argued that it was in an aleukæmic phase, but even then a polymorphonuclear count of 42·7 is rather against this solution.

Leukæmic erythrodermia may be universal, and, as just mentioned, imitate pityriasis rubra, or it may be partial and then resemble psoriasis.

Sequeira and Panton described *lymphoblastic erythrodermia* as distinct from other forms of erythrodermia, especially those of mycosis fungoides, leukæmia and some other cases with enlarged glands, such as the erythrodermie subleucémique described by Cassar and Tapie. It is stated to be characterized by a moderate leucocytosis, 8,000 to 30,000 per cubic millimetre, due to an increase in small lymphocytes which may reach as high as 76 per cent. But it is admitted that such a blood picture resembles that of chronic lymphoid leukæmia, and the distinction relied on by the writers, namely the much higher total white count in chronic lymphoid leukæmia, commonly 200,000 per cubic millimetre, and the higher differential lymphocytic count, often exceeding 80 per cent., do not appear to be convincing. From mycosis fungoides the distinctions given are (*a*) the blood picture, (*b*) the histology, (*c*) absence of a tumour phase, and (*d*) failure to respond to X-ray treatment.

Bronzing of the skin.—Arsenic is so commonly given that pigmentation of the skin would thus be satisfactorily explained, but pigmentation may appear apart from arsenical medication ; thus Hazen records a peculiar bronzing with a slight greenish tinge of the skin over the shoulders, chest, and back of a man before arsenic was given. In connection with bronzing of the skin, it is interesting to note that melanuria without any melanotic growth has been reported in lymphoid leukæmia (Bonnet), and is probably explained by the action of tyrosinase on the oxyphenyl derivatives of the increased proteolysis (Haden and Orr), produced in leukæmia. Further, as Peter suggests, from hepatic insufficiency, which might result from leukæmic infiltration, the liver might no longer carry out its normal destruction of the melanin reaching it.

Urticaria occurs and may accompany miliary leukæmic growths. There may be vesicles, which in a case recorded by Hazen were extremely

numerous, and produced an appearance suggesting dermatitis herpetiformis. Sachs reported a case with a pemphigoid eruption lasting two years.

Chloroma.

Chloroma may be regarded as a form of leukæmia with increased virulence and tumour-formation, especially in connection with bones about the orbits. It is closely connected with acute leukæmia, myeloid and also lymphoid, the latter being said to be the more frequent. It occurs most frequently in males about twenty years of age and runs its course under six months (Dock and Warthin).

The skin may show (i) as in acute leukæmia, purpura, and, as chloroma specially selects the temporal fossa, orbits and skull, hæmorrhages are prone to occur into the eyelids, and may suggest infantile scurvy or the metastases of a malignant growth of the adrenal medulla (Hutchison); (ii) discoloration over subcutaneous tumours, greenish or greyish brown, suggesting the relics of former hæmorrhage; (iii) a diffuse olive tint; (iv) definite green nodules in the skin. Among ten cases of chloroma with skin manifestations collected by Hazen in 1911, there were five with green nodules in the skin. In addition to the cases collected by Hazen, reference may be made to Fabian's case of small hard tumours the size of peas in the skin, to King's probable case, and to Treadgold's case with a tumour in the scalp, described as between the skin and the pericranium; but Treadgold's case would appear to be subcutaneous rather than cutaneous, and a distinction between these two conditions is obviously desirable. It may be noted, however, that in other forms of leukæmia the cutaneous tumours may present a somewhat greenish hue. Tumours arising in the skin in the course of chloroma are apparently very rare.

Multiple Myeloma.

(Synonym: Kahler's disease.)

Multiple myeloma is a rare disease: up to January, 1922, there were only about 77 cases recorded (Meyer and Cajori). In 1911 Hazen quoted 2 cases of probable multiple myeloma, with respectively pruritus and erythrodermia (Spiethoff) and a papular crusty eruption (Bloch).

As in chloroma, tumours in the subcutaneous tissues may occur, and metastatic deposits of calcium, due to decalcification of the bones by the myelomas, may develop, especially in superficial bursæ. The blood does

not show any characteristic change, but Ellermann recorded a case with leukæmia, without, however, any cutaneous manifestations.

Lymphadenoma.

(*Synonyms:* Hodgkin's disease, lymphogranulomatosis maligna, lymphogranuloma.)

Incidence of cutaneous manifestations.—From an analysis of 70 cases of lymphadenoma K. Ziegler estimated that a quarter of all the cases presented at one time or another in their course cutaneous manifestations; among 33 cases, previously unpublished, H. N. Cole found that 13, or 39·3 per cent., had some cutaneous manifestation.

Pigmentation.—Apart from the effects of scratching excited by pruritus or administration of arsenic or X rays, which have led to an appearance like that of a negro, as in Bowen's patient, the skin of the trunk may, as occasionally happens in splenic anæmia and in patients with retroperitoneal tumours, become pigmented. This may be due to irritation of the sympathetic by lymphadenomatous glands surrounding the solar plexus (J. K. Fowler; Nieszkowski), or possibly to adrenal insufficiency brought about by pressure on the adrenal veins.

In Byrom Bramwell's case, in which arsenic had not been given, the pigmentation was like that of Addison's disease; at the necropsy the abdominal aorta was surrounded by enlarged glands, and the pigmentation was explained by irritation of the sympathetic, but pruritus and prurigo had been in existence for two years. In the case of a man reported by Douglas Symmers (85) the skin showed acanthosis nigricans; the cœliac plexus was invaded by lymphadenomatous glands, but the suprarenals were not affected.

Jaundice.—In the cases with relapsing fever the skin has a peculiar icteroid or greyish-yellow tint (Pel; MacNalty). From the pressure of enlarged glands on the bile-ducts jaundice may occur. In the relapsing fever type—the Pel-Ebstein syndrome—jaundice may appear with the febrile bouts and enlargement of the superficial glands, and recede with the disappearance of the fever and the subsidence of the superficial glands. In two examples of this mechanical effect of lymphadenoma under my observation pruritus was absent. Symmers (85), who, in contradiction to the general opinion, believes that lymphadenoma rarely begins in the glands of the neck, and is ten times commoner when the abdominal or the abdominal and thoracic glands combined are affected, found jaundice in 3 out of his 14 cases.

Other mechanical effects of lymphadenomatous glands are œdema of the subcutaneous tissues and cyanosis from pressure on the lymphatics and veins. From impairment of its nutrition the skin may show areas of atrophy.

The hair may change colour, as in Byrom Bramwell's cases, in which it became lighter, finer and more silky to the feel. Loss of hair in association with pruritus has been reported (Weber and Dove; Nanta and Baubru; Colrat), and may be explained as due to inflammatory infiltration around the hair-follicles in connection with the resulting prurigo. Porter described loss of nearly all the hair of the body, but no mention was made of pruritus.

Excessive perspiration may accompany pruritus, but is more often seen in association with fever. The degree of perspiration and fever may not correspond, and profuse sweating has been associated with the close of a pyrexial period in the relapsing fever (MacNalty). Nanta refers to diminished perspiration from a parchment-like state of the skin.

Pruritus.—The incidence of pruritus has been variously estimated; Desjardins and Ford found it in 9 per cent. of 135 cases proved histologically to be lymphadenoma at the Mayo Clinic, K. Ziegler in 8 of his 70 cases, and Cole in 8 out of 34 cases; Favre appears to regard it as constantly present, and Colrat, his pupil, who found it in 11 out of 13 previously unpublished cases, remarks that the past occurrence of pruritus may not be mentioned by the patient unless specially questioned on this point, and this may explain its incidence in only 3 of Longcope's 86 collected cases of histologically proved lymphadenoma. It is much the commonest cutaneous manifestation in lymphadenoma, and is responsible for the next more frequent—prurigo. Pruritus may be the initial symptom of lymphadenoma, and appearing before any obvious glandular enlargement (in from 5 to 12 per cent., Ziegler), may lead the patient to consult a dermatologist in the first instance. It has been compared with the premycotic manifestations of mycosis fungoides (Weber and Dove). It has struck me that the cases with initial pruritus run a rapid course, but this requires more confirmation.

Pruritus may not appear until late in the disease; in a case under Dr. James Collier it came on forty-eight hours before death in a delirious man, who accused the nurses of putting fleas in his bed. The itching may be continuous or intermittent, and appear to correspond with exacerbations of the disease. Like other forms, it may be brought on

by exposure of the skin to heat or cold. Usually it is general, but in rare instances it has been confined to localized areas of the body.

The relation of pruritus to eosinophilia has been much discussed; the almost constant relation of the two has been insisted on (Favre; Mariani), and an analogy has been drawn between l'adénie éosinophilique prurigène and the hydatid pruritus.

In connection with the possible relation between eosinophilia and pruritus in lymphadenoma, attention may be directed to a case recorded by Lortat-Jacob and Solente of lymphadenomatous erythrodermia with 22 per cent. of eosinophils, in which X-rays improved the blood condition, but not the pruritus. Vaccination was followed by suppuration, which is known to cause a diminution of eosinophils, and the pruritus and the cutaneous lichenification and infiltration diminished and the blood became normal for a time, but the pruritus returned. A second suppuration was followed by exactly the some sequence of events, and a third occurrence of suppuration was followed by definite disappearance of the pruritus, though glandular enlargement and the white count increased.

That pruritus and eosinophilia may occur together in lymphadenoma is certain, but it is equally true that pruritus is not necessarily accompanied by eosinophilia or *vice versâ*.

In a man recently under Dr. E. Bellingham-Smith, in St. George's Hospital, in the late stages of generalized lymphadenoma, the leucocyte count was 50,000, with the remarkably high eosinophil percentage of 69. There was no pruritus or skin eruption, but he said that in an earlier stage there had been pruritus; at this period the percentage of eosinophils was 39. In a case I saw in 1910 the percentage of eosinophils was 26, but there was no pruritus.

The cause of the pruritus has given rise to some discussion; on account of numerous analogies it has been thought to be anaphylactic, or to depend on toxic irritation of the peripheral nerve-endings; the poison on this last hypothesis must be blood-borne and not due to local production, for the pruritus often comes on before glandular enlargement is obvious, is not as a rule localized, and the rare lymphadenomatous growths of the skin are not usually itchy. The terminations of the sensory cerebrospinal nerves would naturally appear to be those irritated, but Golay suggests that stimulation of the sympathetic nerves causes pruritus. On the other hand it has been regarded as due to irritation of the central nervous system; Milian and Blum, who thought it was due to a spinal radiculitis and compared it with tabetic pruritus, found a lymphocytosis of the cerebrospinal fluid, though intrathecal injection of syncaine failed to influence the pruritus,

this result thus differing from that of Hervoüet. There is little evidence that the poison is produced in the glands affected, but in Blaschko's case extensive pruritus disappeared two days after enlarged glands were removed and returned when glandular enlargement recurred.

The toxin has been thought to be protein in nature, and derived from leucocytic destruction; but if so, it should be much more frequent and constant in leukæmia than in lymphadenoma, which is certainly not the case. Further, the occurrence of early pruritus, before any lymphadenomatous glands are palpable, shows that there is not any correspondence between the probable amount of cytolysis and pruritus. This would suggest that the pruritus is due to a toxin responsible for the glandular changes rather than to proteins derived from the destruction of lymphoid cells. In other enlargements and hyperplasias of lymphatic glands pruritus is very uncommon. In Desjardins and Ford's 102 cases of lymphosarcoma pruritus was present in 3 only.

Pruritus cannot be correlated with extensive visceral invasion, for example, of the liver, or to the presence of bile in the blood, though Desjardins and Ford found it in two-thirds of their cases with mediastinal lymphadenoma; further, it is difficult to quote any evidence that it is due to a secondary infection. In fact in the state of existing knowledge the occurrence of pruritus appears to be capricious, and possibly to be in part anaphylactic or determined by individual idiosyncrasy; in other words, the responsible factors are imperfectly known.

Prurigo.—A pruriginous eruption is caused by the scratching necessitated by the pruritus, and was specially studied by Dubreuilh under the name of "prurigo lymphadénique," and also by Favre, Colrat and Raynaud, Montpellier and Lacroix. The lesions are purely inflammatory and consist in a small round-celled infiltration around the sweat-glands, there being no histological evidence of lymphadenomatous growth. This prurigo appears to be commoner in men than in women, even allowing for the greater incidence (2·3 according to Desjardins and Ford) of lymphadenoma in males, for of Dubreuilh's 18 cases 4 only were females.

Lichenification and pyogenic infection of the skin are other results of scratching caused by pruritus.

Bullous or pemphigoid eruptions in lymphadenoma are rare; cases have been reported by Bloch, Hoffmann, Yamaski, Königstein. It seems possible to explain the occurrence of a bullous eruption by a peculiar susceptibility of the skin either to the trauma exerted by scratching

or, in the absence of pruritus, to the toxæmia. But it may occur in association with growths in the skin.

Attacks of bullous eruptions with intense pruritus occurred in Corbett and Sibley's patient, who had numerous cutaneous growths.

Universal exfoliative dermatitis or erythrodermia has been reported in a few instances, but, unless supported by histological evidence that the growth is lymphadenoma, such cases are apt to arouse critical suspicion as to their nature and especially as to their relation to mycosis fungoides.

F. P. Weber reported this condition in a man who had suffered from pruritus for a year, and had had enlarged glands for three months. Cases have also been reported by Porter, Wechselmann, Nicolau, Audry, Symmers.

Morbilliform eruption.—Webster reported a case of lymphadenoma which appeared to run its course in sixteen days, and showed a well-marked leucocytosis, 50 per cent. of eosinophils, and a morbilliform rash; no mention is made of pruritus.

Urticaria has been reported (MacNalty); F. Taylor observed a transient patch like *erythema nodosum*; and in rare instances subcutaneous *hæmorrhages* have been recorded (Herringham; MacNalty). In Weber's case recurrent hæmorrhages into the skin and mucous membrane were associated with fever and some necrotic changes in the lymphadenomatous glands.

Lymphadenomatous nodules in the skin are very much rarer than pruritus and prurigo; cutaneous growths with the histological structure of lymphadenoma must be distinguished from prurigo, and it seems probable that this had not always been done in the past, small round-celled infiltration or lymphoid cells being regarded as lymphadenoma. Colrat from a review of the literature accepted three cases only (Grosz; Bruusgaard; Nobl). This is a slight exaggeration of the rarity of true lymphadenoma cutis, but rather to my surprise I have been able to collect twelve cases only.

As bearing on the comparative rarity of true lymphadenoma of the skin, attention may be called to the occurrence of cases of lymphadenoma which appear to take on the character of sarcoma in producing growths outside the lymphatic system. Douglas Symmers (85) has emphasized this by dividing lymphadenoma into two groups: (*a*) the usual run of cases in which the changes are confined to the lymphoid structures, namely the lymphatic glands, spleen, walls of portal vessels, and in the

interstitial tissue of the lungs, kidneys, bone-marrow, subcutaneous tissue and serous membranes, (*b*) in a small number of cases in which, in addition to the above changes, there is continuous infiltration and destruction of muscles, blood-vessels, serous and mucous membranes, erosion of bone and mechanical replacement of solid viscera. It is, however, obvious that Symmers would include the skin growths in the first and not in the second category, in which from their rarity and a desire to explain their occurrence it might be natural to prefer to place them.

There may be either small pin-head-sized nodules in the dermis or of various sizes, large and flattened, or somewhat diffuse plaques. The face and scalp are more often affected than the trunk, and a leonine appearance like that in nodular leprosy may result. The tumours grow slowly, seldom undergo involution or disappear, and very rarely ulcerate spontaneously; in Langley's and Cole's cases, one of a number of cutaneous growths ulcerated. Lyon's case of a thymic tumour with the structure of lymphadenoma perforating the chest-wall, and ulcerating deeply is exceptional, and is of course an example of invasion of the skin by direct continuity, and so rather different from those now under consideration. Whitfield says that they occur late in the course of the disease. As a rule the tumours are not associated with pruritus.

Lymphadenoma cutis must be distinguished from leukæmia cutis by the blood-count, from sarcoma of the skin, and from the so-called sarcoid growths of the skin, which, according to D. Symmers (86), are nearly all tuberculous, though this is perhaps too exclusive a view; some sarcoids, especially those of the Boeck and Darier-Roussy types, are probably, as De Bella suggests, due to some toxic agent other than that of tuberculosis acting on the hæmopoietic system.

Mycosis Fungoides (Granuloma Fungoides).

Mycosis fungoides has been the field of much debate; it has been regarded as the cutaneous form of lymphadenoma. Ranvier (1869) described the microscopic appearances as those of lymphatic tissue, but at this time the histological characters of lymphadenoma, as established by Andrewes and by Dorothy M. Reed in 1892, were not recognized; it is, however, rather remarkable that the view that mycosis fungoides is lymphadenoma cutis has been revived by K. Ziegler (1911). Its relation to leukæmia has also been discussed; it has been described as an

alymphæmic lymphomatosis which may finally present the blood picture of lymphoid leukæmia (Pardee and Zeit ; Strobel and Hazen).

Douglas Symmers (86) concludes that mycosis fungoides is primarily a disease of the hæmopoietic system especially of the lymphatic glands, and that its various skin manifestations are due to toxins manufactured in the glands, or to infiltration of the skin with the same cells as those in the glands ; he allies it both with lymphadenoma and with chronic lymphoid leukæmia. But on *a priori* grounds it would appear reasonable to say that the histological characters of lymphadenoma are quite distinct, and that whether or not leukæmia is present a blood-count can decide.

The clinical resemblance between mycosis fungoides and cutaneous sarcoma may sometimes arise, especially in cases in which the tumours (*d'emblée*) appear without premycotic rashes ; but it has been stated that the absence of Altmann's granules in the cells of a malignant growth and their presence in the cells of inflammatory lesions is a reliable guide (MacCormac).

Mycosis fungoides shows much more definitely than the other diseases included in this discussion the association, though with a chronological separation, of the two groups of cutaneous manifestations, namely (*a*) the toxic, and (*b*) tumours composed of the cells characteristic of the primary disease. Thus we may contrast with it the phenomena of lymphadenoma, in which pruritus and prurigo are relatively common, whereas true lymphadenomatous growths in the skin are exceptional. The pruritus and polymorphic rashes of the premycotic stage first appear, and may recur for relatively long periods, even for ten years (Besnier). Lesions due to scratching, such as papules, pyogenic infection and lichenification, may eventually complicate the erythrodermia, eczematous, erythematous, macular and urticarial changes.

Some of these premycotic manifestations may be confused with leukæmic skin changes; thus Weber, from subsequent microscopic examination of the liver, concluded that a case recorded by Zum Busch as mycosis fungoides was really leukæmic. The premycotic erythema has been described as histologically characteristic (Nicolas, Gaté and Ravault).

A noteworthy feature not present in other diseases presenting these two forms of skin lesions, is that the site of the later tumour formations appears to be largely determined by a preceding patch of the earlier eruptions, though it is, of course, true that *tumeurs d'emblée* without any premycotic cutaneous manifestations may occur. The tumour formations

are an essential part of mycosis fungoides, and thus contrast with the incidence of cutaneous growths in lymphadenoma and leukæmia. The question, however, has been raised if cases of mycosis fungoides ever abort in the premycotic stage, or in other words, if the *homme rouge* stage is curable (Graham Little).

REFERENCES.

(In order to avoid frequent interruption of the text, the numbers indicative of the items in the list of references are only inserted in the text when more than one paper by the same author is given in those lists.)

Introduction.

(1) Audry, C.—*Bull. de la Soc. Franç. de Derm. et de Syph.*, Paris, 1902, xiii, p. 118.

(2) Boudet, G.—"La leucémie aigüe," *Thèse de Paris*, Paris: Steinheil, 1910.

(3) Hazen, H. H.—*Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, p. 532.

(4) King, J. T.—*Johns Hopkins Hosp. Bull.*, Baltimore, 1917, xxviii, p. 114.

(5) Minot, G. R., and Buckman, T. E.—*Trans. Assoc. Amer. Phys.*, Phila., 1923, xxxviii, p. 269.

(6) Pardee, L. C., and Zeit, F. R.—*Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, p. 7.

(7) Sternbebg, C.—*Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1905, xxxvii, p. 437; 1916, lxi, p. 75.

(8) Symmers, D.—*Amer. Journ. Med. Sci.*, Phila., 1924, clxvii, p. 313.

(9) Ward, G.—*Proc. Roy. Soc. Med.*, 1912, v (Med. Sect.), p. 73.

(10) Weber, F. P., and Wolf, F.—*Amer. Journ. Med. Sci.*, Phila., 1916, cliii, p. 231.

(11) Webster, L. T.—*Johns Hopkins Hosp. Reps.*, Baltimore, 1921, xx, p. 251.

Leukæmia.

(12) Arndt, G.—*Derm. Ztschr.*, 1911, xviii, p. 53.

(13) Biesiadecki.—*Med. Jahrb.*, Wien, 1876, p. 233.

(14) Butler, J.—*Arch. Derm. and Syph.*, 1920, ii, p. 594.

(15) Ellermann, V.—*The Leucosis of Fowls and Leucemia Problems*, London.

(16) Ketron, L. W., and Gay, L. N.—*Johns Hopkins Hosp. Bull.*, Baltimore, 1923, xxxiv, p. 404.

(17) *Idem.*—*Arch. Derm. and Syph.*, 1923, vii, p. 176.

(18) Sprunt, T. P., and Evans, F. A.—*Johns Hopkins Hosp. Bull.*, Baltimore, 1920, xxxi, p. 410.

Acute Leukæmia.

(19) Barber, H. W.—*Proc. Roy. Soc. Med.*, 1921, xiv, (Sect. Derm.), p. 10.

(20) Boudet, G.—"La leucémie aigüe," *Thèse de Paris* Steinheil, 1910.

(21) Lavenson, R. S.—*Univ. Penn. Med. Bull.*, Phila., 1908, xxi, p. 178.

(22) Poynton, F. J., and McNee, J. W.—*Trans. Med. Soc. Lond.*, 1923, xlv, p. 100.

(23) Porta, A.—*Relazioni eziologiche e pathogeniche fra certi dermatosi e leucemia*, Piacenza, 1922.

(24) Schultze.—*Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1916, xxxix, p. 252.

(25) Sequeira, J. H., and Panton, P. N.—*Brit. Journ. Derm. and Syph.*, 1921, xxxiii, p. 391.

(26) Shaw, H. B., and Loughlin, D.—*Brit. Journ. Derm.*, 1917, xxix, p. 36.

Chronic Myeloid Leukæmia.

(27) French, H.—*Trans. Med. Soc. Lond.*, 1921, xliv, p. 33.

(28) Ketron, L. W., and Gay, L. N.—*Arch. Derm. and Syph.*, 1923, vii, p. 176.

(29) Rolleston, H. D., and Fox, W.—*Brit. Journ. Derm.*, London, 1909, xxi, p. 377.

(30) Saphier und Seyderheim.—*Münch. med. Wochens.*, 1920, lxvii, p. 69.

(31) Tixier, L., et Troisier, J.—*Gaz. des Hôp.*, Paris, 1910, lxxxiii, p. 171.

(32) Vogel, K. M.—*Nelson's Loose-Leaf System of Medicine*, iv, p. 72.

Chronic Lymphoid Leukæmia.

(33) Arndt, G.—*Derm. Ztschr.*, 1911, xviii, p. 53; and *Journ. Amer. Med. Assoc.*, Chicago, 1914, lxiii, p. 1268.

(34) Audry, C., et Nanta, A.—*Arch. Derm. et Syph.*, Paris, 1918–19, 5e, sér., vii, p. 329.

(35) Bernhardt, R.—*Arch. f. Derm. u. Syph.*, 1914, cxx, p. 17.

(36) Blankenhorn, M. A., and Goldblatt, H.—*Journ. Amer. Med. Assoc.*, Chicago, 1921, lxxvi, p. 583.

(37) Bonnet, P.—*Lyon Chir.*, 1912, viii, p. 582.

(38) Butler, J.—*Arch. Derm. and Syph.*, 1920, ii, p. 594.

(39) Cassar, A., et Tapie, J.—*Ann. Derm. et Syph.*, Paris, 1918–19, 5e sér., vii, pp. 114–122.

(40) Haden, R. L., and Orr, T. G.—*Johns Hopkins Hosp. Bull.*, Baltimore, 1924, xxxv, p. 58.

(41) Hazen, H. H.—*Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, p. 521.

(42) Ketron, L. W., and Gay, L. N.—*Johns Hopkins Hosp. Bull.*, Baltimore, 1923, xxxiv, p. 404.

(43) Peter, J. P.—*Arch. Int. Med.*, Chicago, 1923, xxxii, p. 709.

(44) Sachs, O.—*Wien. klin. Wochens.*, 1921, xxxiv, p. 317.

(45) Sequeira, J. H., and Panton, P. N.—*Brit. Journ. Derm. and Syph.*, 1921, xxxiii, pp. 391–400.

(46) Sweiter, S. E.—*Journ. Amer. Med. Assoc.*, Chicago, 1916, lxvii, p. 1511.

Chloroma.

(47) Dock, G., and Warthin, A. S.—*Med. News*, New York, 1904, lxxxv, p. 971.

(48) Fabian, E.—*Beitr. z. path. Anat. u. z. allg. Path.*, Jena, 1908, xliii, p. 172.

(49) Hazen, H. H.— *Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, p. 531.
(50) Hutchison, R.—*Quart. Journ. Med.*, Oxford, 1907–8. i, p. 33.
(51) King, J. T.—*Johns Hopkins Hosp. Bull.*, Baltimore, 1917, xxviii, p. 114.
(52) Treadgold, H. C.—*Quart. Journ. Med.*, Oxford, 1907–8, i, p. 239.

Multiple Myeloma.

(53) Ellermann, V.—*Ugesk. f. Læger*, Copenhagen, 1923, lxxxv, p. 467.
(54) Hazen, H. H.—*Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, p. 531.
(55) Meyer, A. W., and Cajori, F. A.—*Arch. Int. Med.*, Chicago, 1924, xxxiii, p. 581.

Lymphadenoma.

(56) De Bella, A.—*Giorn. Ital. d. Mal. Ven. e della Pelle*, 1923, lxiv, p. 1053.
(57) Blaschko.—*Derm. Zeitschr.*, Berlin, 1900, quoted by Dubreuilh, *infra*.
(58) Bloch.—*Arch. f. Derm. u. Syph.*, 1907, lxxxvii, p. 287.
(59) Bowen, J. T.—*Journ. Cut. Dis.*, New York, 1913, xxxi, p. 613.
(60) Bramwell, B.—*Clinical Studies*, Edinburgh, 1900, vii, p. 131.
(61) Cole, H. N.—*Journ. Amer. Med. Assoc.*, Chicago, 1917, lxix, p. 341.
(62) Colrat, A.—"L'adénie éosinophilique prurigène (Lymphogranulomatosis)," *Thèse de Lyon*, 1920–1921, No. 282.
(63) Corbett, D.—*Brit. Journ. Derm. and Syph.*, London, 1917, xxix, p. 42.
(64) Desjardins and Ford.—*Journ. Amer. Med. Assoc.*, Chicago, 1923, lxxxi, p. 925.
(65) Dubreuilh, W.—*Ann. de Derm. et de Syph.*, Paris, 1905, 4e sér., vi, p. 665.
(66) Favre.—*Ibid.*, 1918–19, 5e sér., vii, p. 1.
(67) Fowler, J. K.—*Lancet*, 1879, i, p. 258.
(68) Golay, J.—*Ann. de Derm. et de Syph.*, 1922, 6e sér., iii, p. 407.
(69) Herringham, W. P.—*St. Bartholomew's Hosp. Reps.*, 1902, xxxviii, p. 123.
(70) Hervouet, R.—*Thèse de Paris*, 1920–21.
(71) Hoffmann, E.—*Deutsch. med. Wochens.*, 1915, xli, p. 117.
(72) Langley, G. J.—*Brit. Med. Journ.*, 1921, i, p. 667.
(73) Longcope, W. T.—*System of Medicine* (Osler and McCrae), 1915, iv, p. 768.
(74) Lortat-Jacob et Solente.—*Bull. de la Soc. Franç. de Derm. et de Syph.*, Paris, 1923, xxx, p. 309.
(75) Lyon, M. W.—*Amer. Journ. Med. Sci.*, Philadelphia, 1919, clviii, p. 557.
(76) MacNalty, A. S.—*Quart. Journ. Med.*, Oxford, 1911–12, v, p. 70.
(77) Mariani, G.—*Arch. f. Derm. u. Syph.*, Wien, 1914, cxx, p. 781.
(78) Milian et Blum.—*Bull. de la Soc. Franç. de Derm. et de Syph.*, 1920, xxvii, p. 5.
(79) Nanta, A., et Baubru, L.—*Ann. de Derm. et de Syph.*, Paris, 1920, 6e sér., i, p. 145.
(80) Nieszkowski.—*Gaz. des Hôp.*, Paris, 1867, xl, p. 512.
(81) Nicolau.—*Ann. de Derm. et de Syph.*, Paris, 1904, 4e sér., v, p. 752.
(82) Pel.—*Berl. klin. Wochens.*, 1887, xxvi, p. 644.

(83) Porter, J. H.—*Trans. Path. Soc.*, London, 1878, xxix, p. 338.

(83*a*) Raynaud, Montpellier, et Lacroix.—*Ann. de Derm. et de Syph.*, Paris, 1923, 6e sér., iv, p. 74.

(84) Sibley, W. K.—*Proc. Roy. Soc. Med.*, 1914–15, viii (Sect. Derm.), pp. 2, 63–70, 84.

(85) Symmers, D.—*Amer. Journ. Med. Sci.*, Philadelphia, 1924, clxvii, p. 157.

(86) *Idem.*—*Journ. Cut. Dis.*, Chicago, 1919, xxxvii, p. 1.

(87) Taylor, F.—*Guy's Hosp. Reps.*, 1906, lx, p. 19.

(88) Weber, F. P.—*Proc. Roy. Soc. Med.*, 1924, xvii (Clin. Sect.), p. 7.

(89) Weber, F. P., and Dove, P. W.—*Brit. Journ. Derm. and Syph.*, London, 1918, xxx, p. 15.

(90) Webster, L. T.—*Johns Hopkins Hosp. Reps.*, Baltimore, 1921, xx, p. 303.

(91) Wechselmann.—*Arch. f. Derm. u. Syph.*, Wien, 1907, lxxxvii, p. 205.

(92) Whitfield, A.—*System of Medicine* (Allbutt and Rolleston), 1911, xi, p. 604.

(93) Ziegler, K.—*Die Hodgkinische Krankheit* (Jena: G. Fischer, 1911).

Mycosis Fungoides.

(94) Little, Graham.—*Proc. Roy. Soc. Med.*, 1924, xvii (Sect. Derm.), p. 62.

(95) MacCormac, H.—*Ibid.*, 1924, xvii (Sect. Derm.), p. 17.

(96) Nicolas, J., Gaté, J., et Ravault, P.—*Ann. de Derm. et de Syph.*, Paris, 1924, 6e sér., v, p. 257.

(97) Pardee, L. C., and Zeit, F. R.—*Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, p. 7.

(98) Ranvier—In Gillot's *Thèse de Paris*, 1869; quoted in *La Pratique Dermatologique* (Besnier, Brocq, et Jacquet), 1902, iii, p. 527.

(99) Strobel, E. R., and Hazen, H. H.—*Journ. Cut. and Genito-Urin. Dis.*, New York, 1911, xxix, pp. 147, 532.

(100) Weber, F. P.—*Trans. Med. Soc. Lond.*, 1906, xxix, p. 418.

(101) Zum Busch, J. P.—*Derm. Zeitschr.*, Berlin, 1895, ii, p. 204.

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