Papers and Originals

THE SKIN MARKERS OF MALIGNANCY*

BY

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The great advances in scientific techniques have of late overshadowed purely clinical methods of study; in fact, many may say that the day of the clinician is over and that in the near future an electronic computer will give a more reliable diagnosis than the skilled physician. At present diagnosis from clinical observation is still necessary, and in no field of medicine is this more exciting than in the interpretation of skin eruptions associated with visceral disease.

Dr. Watson Smith was himself interested in manifestations of systemic disease in the skin and gave a lecture in Melbourne in 1935 on this subject. It seemed to me appropriate, therefore to choose as a topic for this year's Watson Smith Lecture the occurrence of skin lesions with systemic carcinoma.

It is less than one hundred years since the idea of a skin change which could accompany an internal carcinoma arose. Hebra (1868) described the cachexia of carcinoma and pigmentation of the skin wherever the carcinoma might be. William Frank Smith (1871), in an article on pigmentation, listed pigmentation of the skin caused by cancerous growths of the abdominal viscera, but it is uncertain if this was a personal observation or based on Hebra's paper. In the same year Mitchell (1871) described the case of a woman who developed "a deep bronzing, most intense on the face and on the hands, which looked as though they had been dipped in muddy water and hastily dried, leaving traces of yellow in the creases"—a perfect description. During her illness the patient suffered from an eczematous affection which left deeply stained scars. Necropsy revealed a cancerous mass in the pelvis with metastases in the liver and lungs but no definite primary. The adrenal glands were not involved.

Peutz–Jeghers Syndrome

A paper on the relation of cancer to skin diseases by Gaskoin (1874), although not greatly enlightening as it suggested that the offspring of cancer patients were prone to acne and psoriasis, showed at least that this was a current topic at that time; but it was not until 1890, when both Pollitzer and Janovsky independently described acanthosis nigricans, that the first dermatosis which is constantly associated with internal cancer was recognized. Shortly afterwards Jonathan Hutchinson (1896), who so rarely missed a clinical syndrome, described the cases of twin girls with pigmentation around their mouths. He noted that "they [the pigmented spots] are not in any active sense pathological, we may safely assume, for they remain non-aggressive and the subjects remain in good health." In 1919 Parkes Weber reported that one of the twins described by Hutchinson had died of intussusception.

Peutz (1921) recognized the familial nature of the pigmentation of the lips and its association with polyposis of the gastro-intestinal tract. Nearly thirty years later Jeghers *et al.* (1949) described 10 more cases, and thus the Peutz–Jeghers syndrome was born. The essential skin changes of the Peutz–Jeghers syndrome are pigmented macules that appear in infancy and which may fade or disappear at puberty. The pigmented macules are usually grouped around the mouth, but the fingers, palms, toes, and umbilicus may be involved. In contrast to the skin lesions, which may fade, pigmentation of the oral mucosa remains throughout life. In addition to pigmentation, clubbing of the fingers may be present and scoliosis occurred in 4 of the 21 cases described by Dormandy (1957).

It is important to emphasize that the polyposis in the Peutz–Jeghers syndrome is mainly in the small intestine; thus symptoms arise from haemorrhage, which may be occult and lead to severe anaemia, or from intussusception, which can be recurrent and multiple. Malignant change in the polyps of the small intestines has been recorded (Freeman and Ravdin, 1955; Kutscher *et al.*, 1959), but Dormandy thought that the subsequent course of many of the patients reported as having malignant disease contradicted the histological diagnosis of carcinoma. He is supported in this by Morson (1962) and McKusick (1962), who believe that the polyps are hamartomata. However, polyps may also be present in the stomach, colon, and rectum, and these do not have such a benign course—four of Dormandy's 21 cases, for example, developing carcinoma of the stomach or rectum.

Familial Polyposis of the Colon

Familial polyposis of the colon, which is more liable to malignant change than small-intestinal disease, has been associated with a variety of skin and subcutaneous markers. Gardner (1951) and his associates (Gardner and Richards, 1953; Plenk and Gardner, 1954) described the syndrome of polyposis and subcutaneous bony tumours of the maxilla, mandible, and cranial bones which now bears his name, and Oldfield (1954) noted the association of multiple sebaceous cysts with polyposis in two brothers and a sister, two of whom died of carcinoma of the colon.

Other authors have recorded a variety of subcutaneous benign tumours, such as lipoma (Laberge *et al.*, 1957), osteoma (Weiner and Cooper, 1955), and epidermoid cysts (Gumpel and Carballo, 1956; Staley, 1961), which have appeared prior to symptoms from the colon. The connexion between the mesodermal growths and familial polyposis is presumably a genetic one, but the lesson to be learnt is that if multiple subcutaneous or bony tumours are found the possibility of polyposis of the colon must be considered and sought by investigation.

One of the most fascinating recent genetic studies of a skin lesion and carcinoma was that of Howel-Evans *et al.* (1958), who described two families who suffered from keratosis of the hands and feet (tylosis), an inherited dyskeratosis usually the cause of trivial disability. Among 48 members of these families who were tylotic no fewer than 18 developed cancer of the oesophagus, many early in life, whereas among the 87 members who had not inherited tylosis there was not a single case of oesophageal cancer.

This association had never been described before, nor could it be found in six other tylotic families studied by the authors. The clinical character of the tylosis did not appear to differ from the usual benign disease, and a single

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mutant gene has been suggested to explain this rare happening.

The skin manifestations of an internal cancer consist not only of curious anomalies of mutant genes but of skin reactions such as erythema, pruritus, and blistering, which may occur before, coincident with, or after the neoplasm has become overt. Such skin reactions, termed "non-specific dermadromes" (Wiener 1947), can direct attention to the possibility of cancer and thus lead to early diagnosis and even perhaps in some cases to curative treatment. A knowledge of such eruptions is not, therefore, an exercise in academic erudition but serves a practical and even vital purpose. Since many of the skin reactions occur commonly without an underlying carcinoma, it is necessary to know the frequency of the association for it to be of any practical value; it is with this in mind, and drawing on personal experience, that I wish to discuss some of the other skin markers of carcinoma. Though similar changes may occur with disorders of the reticuloendothelial system, I have limited the scope of my remarks to carcinoma.

Acanthosis Nigricans

From the clinical point of view there is little that can be added to the original description of Pollitzer (1890), who noted the combination of increased pigmentation and hypertrophy which gives rise to a dark, velvety thickening of the skin. This change affects mainly the neck, axillae, and groins, but the umbilicus and nipples are often involved; the colour-changes of the skin lesions varying from brown or black to a yellowish-orange hue which may not be easily noticed. Pedunculated papillomata and flat warts arise in the flexures and on the limbs, and velvety thickening of the palms was considered by MacKenna (1957) to be a useful confirmatory sign. The mucous membranes of the mouth and anus are nearly always affected by a warty overgrowth. The discovery of such changes in an adult—and I stress adult—indicates, as Curth (1943, 1955) has emphasized, that the patient has or will shortly have an adenocarcinoma, which in 90% (Curth, 1948) of cases will be in the abdomen and in 61% (Curth and Aschner 1959) will be situated in the stomach. Wherever the growth arises it is always highly malignant and invariably fatal. Curth *et al.* (1962) have reviewed sections from 42 growths and confirmed that the usual growth is an adenocarcinoma, but the relationship between tumour and skin change, though so definite, is not understood. In many cases the dermatosis may regress after removal of the primary tumour and recur when metastases develop, but recognition of the skin disorder has not so far altered the prognosis.

The name "benign acanthosis nigricans" or, perhaps better, "juvenile acanthosis nigricans" has been given to a skin change which cannot be distinguished either microscopically or histologically from the type associated with malignancy but which is present at birth or appears at the latest at puberty. Inclusion of this group in the statistics for acanthosis nigricans has led to the widely held view (Belisario, 1959) that 50% of the cases of acanthosis nigricans are associated with malignancy instead of the true picture of the adult type where 100% are associated with a neoplasm. It is important to note the age of onset, since the juvenile variety is a familial and harmless disorder, possibly activated at puberty.

A far greater source of diagnostic confusion is the pigmentation and formation of skin tags in the axillae and perineum which occur in obese patients, termed "pseudo-acanthosis nigricans" (Curth, 1951). It was originally described by Arguelles-Casals (1949) and is not uncommon, for six well-marked examples were found among skin out-patients in 18 months in my own department (Tighe, 1960). The absence of mucous membrane changes, the limited area of the acanthotic change, and the usual presence of obesity serve to distinguish it from malignant acanthosis nigricans. Winkelmann *et al.* (1960) have described it in a variety of endocrine disorders, including adrenal insufficiency and diabetes, in which obesity was not invariably present.

Recently Roberts and I (Sneddon and Roberts, 1962) reported a variant of malignant acanthosis nigricans in two patients, both of whom died of carcinoma of the stomach.

The second of these, a man of 58, was referred for treatment of warts on his arms and legs. He had noticed an increase in the number and size of the warts for six months. His only other complaint was lack of energy, The warty growths were distributed in profusion over the front and back of all the limbs but they spared the trunk, and in particular there were no changes in the mouth, axillae, and groins. In appearance the warts were indistinguishable from seborrhoeic warts, and they varied in size from a few millimetres to 1 cm., and interspersed between them were café-au-lait-pigmented macules. He did not complain of dyspepsia, but because of the similarity of this man's warts to the first case a barium-meal examination was carried out which showed a filling defect. Laparotomy confirmed the presence of a large adenocarcinoma of the stomach. We concluded that the lesions were an incomplete form of acanthosis nigricans, but equally well this could be an eruption of seborrhoeic warts which has been described in association with cancer (Gougerot and Duperrat, 1942; Josserand *et al.*, 1948). It is possible that the changes of acanthosis nigricans may be more commonly seen if looked for, and in support of this A. D. G. Gunn and H. Fox (personal communication, 1962) have collected three cases seen in one large general practice within the last year.

Dermatomyositis

It is probable that dermatomyositis, that curious symptom-complex of a skin rash mainly on the light-exposed areas of the body, muscle weakness, and fever, is the end-product of several aetiological mechanisms. Its association with internal malignancy was first noted by Stertz (1916), though until recent years credit for this observation was given to Bezecny (1935). Since that time many case reports have reinforced the view that the association is more than coincidental (Schuermann, 1951, 1952; Caldwell, 1955; Duverne and Plathey, 1957; Sheard and Knoepfler, 1957). From the practical point of view there are a number of questions which need answering. How probable is it that there is an underlying carcinoma? Is it possible that though dermatomyositis is present the carcinoma has not yet developed and therefore curative treatment might be instituted if one knew where to look? Is there any way of differentiating carcinomatous dermatomyositis from those cases which are not so related?

There is wide divergence in the estimates of the incidence of malignant disease; Curtis *et al.* (1952) found eight neoplasms, including reticuloses, in 45 patients with dermatomyositis, but in other series the reported prevalence of neoplasms has varied from 50% in patients over 40 (Arundell *et al.*, 1960) to 6.7% in 270 patients seen at the Mayo Clinic (Christianson *et al.*, 1956). Williams (1959), in a review of the literature, pointed out the possibility of error because cases with an association between dermatomyositis and neoplasm were more likely to be published. He found, however, reports of 92 neoplasms among 590

cases of dermatomyositis (15.3%), and this agrees with Dowling (1955), who reported three neoplasms among 20 cases seen at St. Thomas's Hospital, and my own personal series of 16 patients with dermatomyositis seen in the past 10 years of whom three had carcinomata (Table I). It is perhaps worth stressing that dermatomyositis in children is never linked with malignancy.

TABLE I.—*Dermatomyositis*

Total	Women	Men	Died	Carcinomata
16	13	3	6	3

Carcinomata: 2 in men (prostate, oesophagus) and 1 in woman (stomach).

There are also differences of opinion on whether or not dermatomyositis precedes the neoplasm, but in most of the published case histories the onset of dermatomyositis has occurred before the diagnosis of a neoplasm. The longest interval reported is seven years and the average six months, but Dowling may well be correct in his assertion that the neoplasm is always present, though not diagnosed, before dermatomyositis starts.

Support for the concept that tumour tissue may be responsible for dermatomyositis has come from the work of Grace and Dao (1959), who prepared aqueous extracts of an adenocarcinoma of the breast removed from a patient with dermatomyositis. Skin tests carried out on the patient with the extract gave strong immediate weal reactions, and passive transfer tests were also positive. Curtis *et al.* (1961) have repeated this work with material from a patient with an adenocarcinoma of the lung and have obtained similar positive skin tests. This certainly is valuable evidence that dermatomyositis may also be an allergic reaction to tumour antigen and would explain the occasional favourable response of dermatomyositis to steroid therapy while the carcinoma remains unchanged.

Although Williams (1959) suggested that the type of dermatomyositis associated with neoplasm was more acute and florid with marked sensitivity to light, Dowling (1955) felt that no distinction could be made, and I would agree with this view. The following case emphasizes the difficulty both of diagnosis and of management.

A 62-year-old housewife was admitted to hospital in May, 1957, with a florid erythema of the face, forearms, and hands of four months' duration. Three weeks before admission she had developed generalized muscle-weakness and difficulty in swallowing. On examination the skin eruption was classically that of dermatomyositis and the patient was unable to lift herself from the bed; there was marked loss of power in the arms and legs. The diagnosis was confirmed by a muscle biopsy and demonstration of increased creatine and creatinine excretion. She responded well to treatment with prednisolone and A.C.T.H.; power returned to her muscles, the rash faded, and she was discharged home on a maintenance dose. No evidence of a neoplasm was found, though barium studies of the whole gastro-intestinal tract were not made. On September 2, 1957, she died at home, the certified cause of death being pulmonary embolism from thrombosis in the legs. Inquiry of the coroner, however, revealed that an early carcinoma of the stomach had also been found, and it seems possible that this carcinoma was present nine months previously, when her symptoms began.

This case history also underlines the fact that more neoplasms are likely to be discovered if they are searched for, and this has been noted by Arundell *et al.* (1960), who found that more carcinomata were discovered in patients with dermatomyositis seen in the years 1949–59, when clinicians were aware of the association, than in the previous 10 years.

The presence of a neoplasm in at least one in six patients with dermatomyositis suggests that investigation of such cases must be comprehensive, and according to Williams (1959) the sites most likely to be affected are the stomach, breast, lung, and ovary.

Improvement in dermatomyositis has followed surgery and radiotherapy, but, as Dowling (1955) pointed out, the majority of these patients die of dermatomyositis and only rarely of carcinoma. Rather disappointingly I can find no example in the literature of complete cure of dermatomyositis and the underlying neoplasm.

It seems generally agreed that in contrast to dermatomyositis there is no association between scleroderma and malignancy. Schuermann (1951) found no references to this in 600 published cases, and Dowling (1955), Curth (1955), and Belisario (1959) all comment on its rarity. A recent survey of 727 patients with scleroderma also disclosed no evidence of relationship with cancer (Tuffanelli and Winkelmann, 1961).

Figurate Erythemata

Closely allied to dermatomyositis are the figurate erythemata; erythema gyratum repens and erythema figuratum perstans are two of the names often used. Gammel (1952) first described the case of a woman with an eruption of irregular wavy bands of erythema and marginal desquamation which covered her whole trunk; the bands of erythema and scaling moved constantly at the rate of 1 cm. a day, and the appearance was aptly likened to the graining of wood. A small adenocarcinoma was found in her left breast, and after its removal the eruption which had been present a year cleared in 10 days.

Purdy (1959), when faced by the problem of a woman patient with an identical eruption, recalled Gammel's case and discovered a small breast tumour which proved to be a duct carcinoma. Surgical removal of the tumour produced clearance of the eruption in two weeks.

Gold (1959) showed a man at the Royal Society of Medicine with a similar eruption. At the onset of the rash the sedimentation rate and chest *x*-ray picture were normal, but some four months later *x*-ray changes suggestive of a carcinoma of the bronchus appeared. In this case also the rash faded after the neoplasm had been treated by radiotherapy. A 75-year-old man with a bizarre annular erythema on the trunk associated with an inoperable carcinoma of the stomach was shown to me some years ago by my colleague, Doris Fletcher. It is not possible to assess the relative frequency of the association from the few published reports, but although the cases of gyrate erythema are rare they should be investigated fully, since the skin eruption appears to be an allergic reaction either to infective agents, such as fungi (Jillson, 1954), or to tumour tissue. Confirmation of the latter was achieved by Shelley and Hurley (1960) in a remarkable patient, a young woman with a generalized migrating gyrate erythema which differed from the previous examples in that the gyrations were firm cords rather than simple erythema. They showed that the serum of this woman, who had marked breast hypertrophy, contained an auto-antibody to the cystic breast tissue. Excision of the excessive breast tissue produced improvement in the skin eruption, which thereafter was controlled completely by a low dose of corticosteroids.

Although such auto-antibodies have not been demonstrated yet in patients with a malignant tumour, Shelley (1962) believes they may be present. Such a mechanism may also explain the fixed erythematous eruptions suggestive of chronic or even disseminated lupus erythematosus commented on by Forman (1952). The onset of an L.E.-like rash in a patient past middle age, particularly

a man, should direct attention to the possibility of a carcinoma which in my experience is most frequently in the lung. Forman has also drawn attention to vascular changes of palmar and facial telangiectasia, more usually associated with liver disease, in two cases of carcinoma of the lung. More dynamic vascular changes may be seen in association with carcinoid tumours: in the very few examples of this condition I have seen, the paroxysmal flushing of the skin has not been striking and has not led to the initial diagnosis: usually this has been suspected on other grounds, and the flushing has been noted when looked for subsequently. Nevertheless, attacks of flushing of the face, limbs, and body with telangiectasis and persistent cyanosis should arouse suspicion of metastatic carcinoid growths.

Bowen's Disease

Yet another marker of internal malignant disease was discovered by Graham and Helwig (1959) when they observed that cases of Bowen's disease (intra-epidermal carcinoma) were more likely to develop an internal carcinoma than the general population. Bowen's (1912) disease had been considered until then a chronic dermatosis, which in itself was precancerous but which would give rise only to a localized squamous neoplasm of the skin. The manifestation in the skin is a scaly eruption spreading very slowly and resembling either a patch of psoriasis or eczema. Graham and Helwig (1961) found that of 155 cases of Bowen's disease 37 (23.9%) developed a carcinoma of some internal organ within an average time of five and a half years after the diagnosis of Bowen's disease. Epstein (1960) also found that 15% of 33 patients with Bowen's disease had a visceral malignant tumour. Similar findings were reported by Peterka *et al.* (1961), who noted that if Bowen's disease affecting the covered parts of the body was considered 11 of 33 patients developed an internal carcinoma within six years, while among 20 patients with lesions on the face, neck, and hands only one was found to have an internal tumour. They suggested, however, that the greater difficulty of diagnosis of Bowen's disease when occurring on exposed areas might explain the discrepancy. I have myself followed up nine patients with Bowen's disease on the covered parts of the body seen since 1953. The diagnosis of Bowen's disease was made on clinical grounds and later confirmed by histology. Of the nine cases five have since developed internal carcinomata (55%) (Table II). These figures are so small that they are probably not significant, but B. Russell (personal communication, 1962), working on the same problem, has found 11 patients with keratoses and Bowen's disease of the covered parts of the body, six of whom have developed carcinomata (54%), whereas of 320 patients with lesions on the exposed parts only 4.4% developed systemic malignancy.

TABLE II.—*Bowen's Disease*

Year	Sex	Age	Site	Carcinoma
1953	F	80	Chest	No
1960	F	57	,,	,,
1954	F	48	Pubic region	Carcinoma colon, 1956
1956	F	60	Lumbar region	No
1954	F	67	Shoulder	Carcinoma stomach, 1960
1959	M	66	Back	Bronchial carcinoma, 1961
1953	M	60	Penis	No
1960	M	52	Chest	Bronchial carcinoma, 1962
1961	F	56	Trunk	Carcinoma caecum, 1962

The similarity of Bowen's disease and arsenical keratoses suggests that arsenic must be considered as a possible common factor in the causation both of Bowen's disease and of the internal neoplasm. In two of my patients with carcinomata, one a case of psoriasis and the other an epileptic, there was a history of arsenical medication many years previously but no history in the others. I am doubtful whether arsenic is therefore important in every case, but Graham and Helwig (1961) claimed that arsenic was found in 90% of their cases of Bowen's disease in skin and in only 43% of controls. It has been shown by Sommers and McManus (1953) that 37% of 27 patients with arsenical carcinoma of the skin had internal carcinoma, and Roth (1957) found 16 cancers in 27 Moselle vintners with chronic arsenical poisoning. It would appear from the figures so far available that between one-third and one-half of patients with Bowen's disease on the covered parts of the body will develop an internal carcinoma between 5 and 10 years after the initial diagnosis. Inorganic arsenic has been prescribed by dermatologists for many years for a number of dermatoses. The high incidence of systemic malignancy in Bowen's disease and arsenical skin carcinoma should now put an end to its use.

Other Associated Skin Eruptions

The conditions so far discussed are unusual enough to make one alert to the possibility of internal malignancy when they are diagnosed. Many other skin eruptions have been reported in association with internal neoplasia, but such association is an infrequent one and may well be coincidental. Generalized itching (Rothman, 1925; Vehave, 1926; Wiener, 1947), a common symptom in the skin department, is only very rarely linked with an internal neoplasm. Erythema multiforme and urticaria are such common diseases that as clues to cancer they are not helpful, but both have been described in association with carcinoma and have cleared when the tumour has been removed (Davis, 1922; Urbach, 1942). Exfoliative dermatitis is more often a forerunner of reticuloses but has been recorded in patients suffering from carcinoma of the lung (McGaw and McGovern, 1956). It is easy to conclude erroneously that two relatively common conditions may be linked, and this association is as yet not confirmed.

A number of blistering eruptions have been reported in patients with malignant tumours. Small grouped irritable blisters, indistinguishable from dermatitis herpetiformis, have been described in association with carcinoma of the labium (Bogrow, 1909), cancer of the uterus (Hartzell, 1918), chorioncarcinoma (Elliott, 1938), hydatidiform mole (Tillman, 1950), and carcinoma of the ovary (Tobias, 1951). Erythema-multiforme-like rashes have occurred usually after deep *x*-ray therapy (Arnold, 1949; Mazzini and Blasi, 1953), the eruption presumably being due to allergic reaction to necrotic tumour cells. Such necrosis may occur in tumour tissue without radiation and may be another mechanism in the production of skin eruptions. From time to time cases are reported in which frankly bullous lesions coincide with the discovery of a carcinoma (Forman, 1960). Such a patient was presented to the Royal Society of Medicine by J. M. Marks (1961) for Dr. Gold. This patient, a woman, had suffered from a sparse blistering eruption on the body and marked blistering in the mouth for four years. Soon after the onset a malignant melanoma was removed from her back. The eruption in the mouth persisted, but the skin lesions were controlled with steroids until a secondary deposit arose in an axillary gland. After removal of the gland the skin eruption was more easily controlled. In the discussion of this case three other patients with pemphigoid affecting the buccal mucosa and carcinoma were cited (Wilson, 1961; Gold, 1961), and I have seen this association in a man with a gastric neoplasm. This patient developed bullous skin lesions and changes

similar to ocular pemphigus, including conjunctival adhesions, coincident with widespread abdominal metastases. A similar occurrence with carcinoma of the bronchus, diagnosed I think incorrectly as ocular pemphigus, has been published (Chadfield and Kanagasundaram, 1962).

There is thus evidence that subepidermal blistering eruptions do occur in patients with carcinoma more frequently than by coincidence and that when they do they are more likely to affect the mucosae than the usual variety of senile pemphigoid. Such affection of the mucosae resembles most closely ocular pemphigus.

Conclusion

I cannot end without a reference to cutaneous metastases. It is perhaps surprising that these affect only 1–3% of patients with cancer (Wiener, 1947). Neoplastic cells must certainly reach the skin capillaries, yet only very few seem to thrive. While diagnosis of the majority is simple, secondary nodules on the scalp can closely simulate sebaceous cysts or harmless adnexal tumours of the epidermis and may be overlooked.

The conditions which have been discussed are uncommon, but they are not very uncommon, and it is probable that most physicians and dermatologists will see the majority of them in a decade of practice. My hope, therefore, is that this review of the skin markers of malignancy will prove of practical value.

Summary

In the last hundred years the association of skin eruptions with systemic malignant disease has been increasingly recognized. Skin changes can be divided into genetic abnormalities, which coincide in certain families with a high incidence of internal carcinoma, and other eruptions whose causes are as yet unknown. The clinical features of acanthosis nigricans, including recent personal observations on a forme fruste, are described and its significance is discussed.

A carcinoma or reticulosis will be found in one in six patients suffering from dermatomyositis; it is probable that the carcinoma is present though not giving rise to symptoms when the muscle-weakness and rash appear. Evidence is quoted to suggest that dermatomyositis is an allergic reaction to the presence of tumour tissue; a similar explanation would account for the gyrate erythemata which may also appear before a carcinoma becomes overt. The frequent occurrence of internal neoplasia in patients with intra-epidermal carcinomata (Bowen's disease), first reported in America, is supported by personal observations. The more unusual skin manifestations of malignant disease are reviewed in order to draw attention to the diagnosis of malignant disease by their recognition.

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