including filariasis, in Keneba, a village of 710 population in the West Kiang District of the Gambia Protectorate.

A preliminary survey showed that of 603 persons present 220 carried microfilariae of *W. bancrofti* and 203 carried microfilariae of *A. perstans*. Treatment was directed primarily against *W. bancrofti*.

Hetrazan, in five daily doses of 5 mg. base per kg. of body weight, was administered to 181 villagers in February, 1951. Of these, 69 had microfilariae of *A. perstans* as well as of *W. bancrofti*.

Re-examination ten months after treatment showed that 64% of those treated were free of microfilariae of *W. bancrofti*, and that the total microfilariae in all those originally found infected had been reduced by 94%.

Microfilariae of *A. perstans* had been eliminated from the blood of 72% of those treated, with a 92% reduction of total load; in untreated persons the microfilariae of *A. perstans* had disappeared spontaneously in 32%, but the total microfilaria count had increased by 49%.

Unpleasant side-effects attributed to hetrazan were spontaneously reported by one-quarter of those treated. These disorders were common and severe enough to make the drug very unpopular, and it was only with great difficulty that the trial was completed, in spite of the exceptionally favourable circumstances in which it had been started.

The conclusion was reached that, in spite of the very high therapeutic efficacy of hetrazan, its common toxic effects and high cost are disadvantages which seriously prejudice the chances of its successful use for mass treatment in areas, such as this, where filarial sequelae are rare and the people have no consciousness or fear of the disease.

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A short account of the French Prosthetic Service for the nation's war disabled is given by Lieutenant-Colonel C. Abadie, medical director of the service, in the October issue of the *Rehabilitation Bulletin* of the World Veterans Federation. Appliances are supplied at State expense so long as the patient requires them. He is free to choose his appliance among the recognized types that suit his disability. The State also pays for repairs, which are mainly carried out at workshops in the service, and for replacements when required. Amputees are entitled to two appliances, identical or dissimilar in type, for each limb amputated. In addition to appliances, severely disabled war victims may receive a hand-propelled wheel-chair of one kind or another, and the State is responsible for the upkeep and repair. A pensioner with a head wound that has led to permanent baldness has a right to a wig, which can be replaced every three years.

THE SKIN MANIFESTATIONS OF MALIGNANT DISEASE

WITH SPECIAL REFERENCE TO VASCULAR CHANGES AND DERMATOMYOSITIS*

BY

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Deposits of carcinoma in the skin usually occur late in the course of the disease. They are often few in number, and the diagnosis is established by excision and section. Of more interest to the dermatologist are the non-specific skin manifestations which can be related to the presence of a carcinoma.

When a visceral carcinoma is well advanced the skin may be pale, inelastic, and yellow in tint, without jaundice. These changes may be due to lack of appetite, diminished food intake, and difficulty in assimilation. Thus a carcinoma of the stomach or intestinal tract may interfere with iron and vitamin absorption. It is not unusual to see an atrophic dermatitis of the exposed areas of the face and arms comparable to the changes of pellagra, no doubt due to deficient intake or utilization of vitamin-B₂ complex.

Cochrane and Alexander (1951) described the case of a woman with an advanced carcinoma of the lower end of the oesophagus, who was found to have a generalized thickening and dryness of the skin, tongue, and mouth, besides numerous warts and pigmentation. With vitamin-A therapy, 700,000 units a day by mouth, "there was subjective improvement in the itching, and the skin felt much less coarse and more pliable."

As well as the nutritional deficiencies, the skin may be affected by toxic substances derived from the tumour, with degeneration of the connective tissue comparable to senile elastosis. When the liver is infiltrated the raised blood cholesterol will also contribute to the yellow colour.

Itching

The demands of rapidly growing malignant tumours on amino-acids and essential substances—for example, folic acid—may contribute to the deficiencies shown by the skin. Irritation or pruritus is the most common cutaneous symptom of malignancy, and is usually generalized. A rarity is the localized itching of the nostrils with some tumours of the brain. Itching occurs with carcinoma of the abdominal organs and of the thorax, and with Hodgkin's disease and the leukaemias. Pruritus may follow the x-ray treatment of an abdominal carcinoma or of a tumour elsewhere. This would suggest that a reaction comparable to a sensitization reaction occurs to protein substances released by degenerating cells. One may recall the pruritus and urticaria which have been observed following haematomata due to injury.

With the complaint of itching, inspection may reveal small, irritable, skin-coloured papules which usually disappear after the tops of the papules have been excoriated. Occasionally, however, these papules have been noted to persist, to enlarge, to ulcerate, and to display a neoplastic histology. This clinical observation has led to the suggestion that the transitory papules are an expression of a vital reaction on the part of the skin to single cells of the tumour. It is difficult not to concede that tumour cells must invade the circulation and may fail to establish themselves in the

*Lecture given at the Institute of Dermatology, St. John's Hospital for Diseases of the Skin, on January 15, 1952.

skin or be destroyed by a local mechanism, with the production of histamine-like substances with itching. If the embolized tumour cells are in larger numbers they may survive and produce a carcinomatous nodule. It is certainly true that secondary nodules are seen in the skin in only a small proportion of cases of carcinoma.

Widespread dermatitis has been encountered during the course of an advanced carcinoma. The distribution on the trunk flexures and scalp leads to the suggestion of a seborrhoeic dermatitis. The dermatitis is to be regarded as a manifestation of a deficiency, and liver by mouth or injection and vitamin-A and -B therapy are indicated.

The bullous dermatoses, including the grouped smaller blisters of dermatitis herpetiformis, have occurred with sarcoma of the thyroid (Rothman, 1925), and with a chorion carcinoma (Elliott, 1938).

Elliott's case is of interest. A woman aged 43 developed, two years after a hydatidiform mole, itching papular and vesicular lesions healing with pigmentation, and blisters on normal skin and in the mouth. The attacks seemed to be controlled with arsenic. The urine gave a positive pregnancy reaction. X-ray examination showed a secondary deposit in the lung. She died 27 months after her first bleeding and three months after her first cutaneous manifestations. These occurred about the time that the uterus was observed to enlarge with the increased activity of the malignant growth.

In a chorion carcinoma the increased production of hormones from the growth may be of significance in the development of the rash. The increased gonadotrophic hormone is responsible for the positive pregnancy reaction given by the urine, and it would be of interest to see if those patients with herpes gestationes which persist after delivery show evidence of similar endocrine activity.

Vascular Changes

The vascular changes which may be met with in the skin with visceral malignancy form an uncommon but dramatic group.

The localized angiomas and spider naevi when appearing suddenly in middle age have been thought to be due to a carcinoma, although any statistical evidence is lacking. Angiomas and spider naevi are to be found over the face and trunk with increasing incidence at the menopause in males and females; that is, when the incidence of carcinoma rises. Their occurrence can be related to alterations in hormone blood levels.

These spider naevi over the face and chest are common during pregnancy. In a case with well-marked telangiectasia of the face, neck, and arms, associated with each of 11 pregnancies, the dilated vessels appeared at the end of the first month of pregnancy and disappeared within five days of the delivery of a dead foetus (Forman, 1933-4). They are also met with in association with cirrhosis of the liver and pulmonary disease.

There would appear to be certain capillaries capable of hypertrophy and even of new growth, angiomas, under the influence of altered hormone levels, both of androgens and of oestrogens.

Telangiectasia

Discrete capillary dilatation over the face with more diffuse palmar telangiectasia may be found with cirrhosis of the liver and pregnancy, and also, I believe, with pulmonary disease when there is congestion of the liver. The telangiectasia is best seen over the thenar and hypothenar eminences, and the colour changes when the hands are dependent.

Bean (1943) has pictured the distribution of the palmar and digital erythema in 11 cases in his article on acquired palmar erythema and cutaneous vascular "spiders." The following case histories are of two of my patients with palmar erythema and telangiectasia of the face.

Case 1.—A gas-fitter, aged 65, in 1943 had a new growth removed from the thigh with block dissection of the lymphatic

nodes, which were free of growth. The growth was said to be an "endothelioma." In 1945 he complained that he had been becoming weak and had had difficulty in swallowing. The knee-jerks were absent. The hippuric acid liver-function test was done three times, twice by the oral and once by the intravenous route. All results were low, showing diminished liver function. The patient was generally weak. He had a large number of vascular spiders peppered over his face, forehead, neck, and upper chest. They were also present on the arms, hands, and knees. There were many red angiomas (De Morgan spots) on the abdomen and thorax. A striking erythema was present on the palms in the typical distribution and on the soles of the feet. He died after having recovered from an anaesthetic given for oesophagoscopy. The essential post-mortem findings were: Heart, myocardial fibrosis. Thyroid, small and atrophic. Suprarenal glands, left, small adenomata on the surface, medulla not clearly defined; right, cortical hyperplasia. Both glands felt very firm and woody, and were of normal size. Liver smaller in size than normal: section—fibrosis present, with congestion. An enlarged mediastinal gland was sent for section and was returned as containing a deposit of oat-celled carcinoma.

Case 2.—A man aged 58 was found to have a secondary carcinoma in a rib and a (?) primary in the bronchus. While in hospital he developed spider naevi on the face and forehead and the characteristic palmar erythema, which persisted until death. Post-mortem examination showed a massive metastasis in the liver and nodules of carcinoma throughout both lungs.

The erythema of the palms resembled that described by Bean, but the considerable muscle weakness in the first case is a link with the dermatomyositis group to be described below. In both cases there was a circulatory deficiency and liver damage. The liver is known to destroy, modify, or neutralize oestrogens and androgens. The increased level of oestrogens or 17-ketosteroids due to liver disease has been held by Bean to be responsible for the telangiectasia which occurs in people with susceptible blood vessels.

Localized Erythema

Localized erythema with hyperkeratosis, resembling lupus erythematosus, has been described with carcinoma. The following case is of this type.

A man, aged 39, had in January, 1939, areas of redness and hyperkeratosis on the ears, scalp, fingers, and chest. On the chest there was an erythema with central atrophy. Small buff-coloured papules were shown at the periphery when the skin was stretched. He complained of the passage of blood and mucus from the bowel, but no carcinoma was discovered. Section of the skin showed a condensation of papillary connective tissue and capillary dilatation. One and three-quarter years after the rash appeared he died out of hospital with a diagnosis of inoperable carcinoma. No post-mortem examination was made.

A more generalized erythema with telangiectasia and atrophy has been observed with a proved carcinoma of the uterus.

A married woman, aged 68, first had erythema on the upper arms, face, and hands in March, 1946. By August there was a bright erythema of the face, eyelids, and scalp. The neck was affected where exposed to light and showed telangiectasia. The upper arms, backs of the forearms, and backs of the hands showed a fixed telangiectatic erythema with superficial atrophy, this being particularly marked on the upper arms. Over the lower lumbar region there was a small firm nodule. Biopsy of the nodule showed a cellular anaplastic tumour infiltrating freely, indicative of a high grade of malignancy (Dr. S. Navasquez). Biopsy of skin of the upper arm showed that the capillaries had surrounding oedema and lymphocytic infiltration, and the collagen bundles were separated and fragmented. Biopsy of deltoid muscle showed no myositis. In September, 1947, a carcinoma of the cervix was demonstrated.

Carcinoma Associated with Dermatomyositis

The most dramatic of the erythematous reactions in this group occurring with carcinoma are the cases of dermatomyositis. Bezecny (1935) recorded two cases in which the relationship between dermatomyositis and ovarian carcinoma was established.

A woman aged 58 had for six months had a rash which had begun with an erythema of the face, scalp, neck, and hands.

Pains in the arms and muscle weakness developed later. The musculature was affected so that she could not turn her head. The neck muscle, masseters, and the pectorals were tense and tender, and nodular infiltrations could be felt. Swallowing was difficult. The scalp and eyelids were affected and there was a diffuse alopecia. Three months later an operation was performed for large bilateral tumours of the ovaries. The surface of the ovaries and adjoining peritoneum showed carcinomatous metastases. Even a few days after the operation she was able to swallow solid food. Four months after the operation movement of the neck and swallowing had returned to normal. The facial skin was pale and there were occasional telangiectases over the temples and metacarpo-phalangeal joints.

Bezecny described a second case of a woman with an ovarian carcinoma associated with dermatomyositis. Eleven days after the operation there was great improvement in the skin and muscles.

The following three cases, personally observed, are examples of this association:

A woman aged 60 years had an inoperable carcinoma of the breast and developed erythema of the back, the backs of the hands and fingers, the extensor aspects of the forearms, and the ankles. There was also definite weakness of the shoulder muscles. The erythema faded after two months, leaving atrophy and pigmentation.

A woman aged 51 years had a gland removed from the left side of the neck in July, 1937. This was found to contain a squamous-cell carcinoma. It was suggested that the primary was in the lower oesophagus, but this was never proved. In October, 1937, she developed an erythema of the face, ears, and hands. She had been given deep x-ray treatment. When seen in December, 1937, she had developed weakness of the shoulder-girdle muscles and difficulty in speech and swallowing. Over the whole face, neck, shoulders, and front of the chest the skin was erythematous and cyanotic, particularly over the eyelids, and there was an erythema over the forearms and backs of the hands. Subsequently the erythema faded and the weakness of her shoulders improved. Her general condition deteriorated, however, and she developed a mass in the pelvis, probably secondary deposits. A few months later she died. Section of the skin and deltoid muscle showed a thin epidermis, oedema, and fragmentation of the collagen bundles. The muscle bundles were atrophied and tortuous, with multiplication of the sarcolemmal nuclei.

A man aged 62 years had had a partial gastrectomy for a gastric carcinoma a year previously. Six months later he developed an erythema of the face, swelling of the eyelids, and erythema of the hands and forearms. A month later there was loss of hair, difficulty of speech and swallowing, and weakness of the shoulder-girdle and buttock muscles. Shortly before he was seen there had been a recovery of power, swallowing had become possible, and the erythema had faded. There was considerable wasting of the shoulder muscles, the skin of the face and orbits was telangiectatic and pigmented, and similar changes were noted on the back of the neck, shoulders, and buttocks. Subsequently he developed a painless obstructive jaundice.

Acanthosis Nigricans

Lastly, reference may be made to the proliferative epithelial changes known as acanthosis nigricans, the association of which with carcinoma of the abdominal viscera or of the bronchus has been found in a high proportion of cases over the age of 40. Even in cases under 30 years the prognosis must be reserved. The hypertrophy affects the skin, particularly of the flexures, and mucous membranes. The cases in which there is no malignancy tend to pigment less, and most of them occur in the years of puberty.

An interesting case of a girl aged 13 with acanthosis nigricans was recorded by Watson Smith (1933). The skeleton was overdeveloped, with a large jaw, hands, and feet. Her height was 5 ft. 11 in. (180 cm.) and her weight 11 st. 4 lb. (71.7 kg.). She grew a profuse beard of fine lanugo hairs and her arms and legs were unusually hairy. There was thus evidence of anterior pituitary and adrenocortical overactivity. Kok (1951) recorded an interesting case of acanthosis nigricans in a patient with cirrhosis of the liver and discussed the role of the consequent metabolic and endocrine changes.

Discussion

In the above account of the erythematous and telangiectatic changes evidence is given of parallel manifestations due to endocrine changes—for example, in pregnancy and the menopause—and to liver dysfunction. One must consider whether there is a similar alteration in hormonal blood levels in those cases of erythema, telangiectasia, and dermatomyositis occurring during the course of a carcinoma. Further, there is a possibility that a period of altered hormone levels may be a factor potentiating or activating a carcinoma. Certain work may be mentioned in support of this view.

Thus oestrogens injected into certain strains of male rats give rise to carcinoma of the breast, and in female mice to carcinoma of the uterus (Payling Wright, 1950). Chemical substances with a structure similar to hormone steroids—for example, anthracene—when given by mouth in rats produce carcinoma of the lungs. The incidence of the induced carcinoma was of statistical importance (Payling Wright, 1950). The common carcinomata in women are those affecting the breast, uterus, and ovaries—structures which are particularly sensitive to hormonal effects. A myopathy with muscle changes similar to those of dermatomyositis has been recognized in some cases of hyperthyroidism.

However, the telangiectatic element of the cutaneous reaction would be expected to appear early in the course of a neoplasm if the latter were induced by endocrine changes. In the above cases in which blood vessels, connective tissue, and muscles were involved, the signs appeared late in the course of the malignancy.

One must therefore assume that if altered hormone levels are of importance in these vascular, connective tissue, and muscle changes, these occur during the course of a neoplasm for the following reasons: (a) malignant invasion of the liver, disturbing its regulating function on hormone blood levels; (b) carcinomatous tissue itself may produce a chemical substance with an effect on blood vessels and connective tissue (Bezecny, 1935); and (c) certain carcinomata—for example, ovarian carcinoma—may themselves produce hormone steroids or may induce altered pituitary activity.

Summary

The "cachectic" skin is observed particularly in relation to malignant disease of the gastro-intestinal canal. The skin is dry, inelastic, scaly, pale, and yellow.

These changes are due in part to disturbance of digestion and absorption of iron, protein, and accessory food substances. The yellow tint may be in part due to degenerative changes in connective and elastic tissue. These deficiencies may occasionally lead to a chronic dermatitis.

Pruritus is a frequent symptom of carcinomas, reticuloses, and leukaemias. The suggestion is made that this is due to a sensitization to the altered protein of the malignant tissue or possibly follows on the destruction of malignant cells in the skin.

The rare bullous reactions, resembling dermatitis herpetiformis or pemphigus, may be caused by a similar mechanism. Dilatation of the capillaries—localized as spider naevi or angiomas, or diffuse telangiectasia of the palms and soles—has been observed with carcinoma.

Again localized capillary dilatation and alteration in the connective tissue, leading to clinical changes resembling lupus erythematosus and scleroderma, forms a link between simple telangiectasia and dermatomyositis occurring with carcinoma.

Consideration has been given to the possible role of hormones in the aetiology of the vascular dilatation and mesoblastic tissue degeneration. Thus alterations

of hormone levels with pregnancy may explain the telangiectasia of the face and chest, reversible after parturition.

Disease of the liver, with disturbance of its ability to regulate oestrogen and androgen blood levels, has been known to be associated with telangiectasia of the face and palms, and occasionally with enlargement of the male breasts.

A myositis may be an early sign of thyrotoxicosis.

At some stage in their course malignant tumours of the genital organs—for example, the ovaries—may themselves produce steroids capable of affecting vessels and connective tissue.

Acanthosis nigricans in which there is hypertrophy and pigmentation of the skin, in adults, is in most cases associated with malignancy. The maximum incidence of the benign cases is at puberty, and in one case quoted there was additional evidence of endocrine disturbance (acromegaly and virilism).

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EFFECTS ON FOETAL WEIGHT OF GROWTH-HORMONE-CONTAINING ANTERIOR PITUITARY EXTRACTS GIVEN TO PREGNANT RATS

BY

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It has long been recognized that pregnancy in women suffering from diabetes mellitus is associated with a high foetal mortality rate and the tendency to foetal gigantism. It is now well known that pregnancy in women who subsequently develop diabetes mellitus is also associated with these features, but in lesser degree (Miller *et al.*, 1944; Miller, 1945; Henley, 1947; Barns and Morgans, 1948; Gilbert and Dunlop, 1949; Gilbert, 1949). This pre-diabetic phase is probably of some fifteen years' duration (Barns and Morgans, 1948).

It has been suggested that excessive production of the diabetogenic-growth hormone by the maternal anterior pituitary gland may be responsible for the large foetuses in pre-diabetic and diabetic pregnancies and also for the subsequent development of the diabetic syndrome in the pre-diabetic woman (Barns and Morgans, 1948; Gilbert, 1949). Further, the overactivity of the maternal anterior pituitary gland may be responsible for the high foetal

mortality rate (Barns and Morgans, 1948). Experimental studies in rats suggested the possibility that excess of the diabetogenic-growth complex itself may be the factor responsible for the foetal deaths (Barns *et al.*, 1950).

The present investigation has been undertaken to see whether there is any experimental support for the suggestion that an excess of the diabetogenic-growth factor causes foetal gigantism. In it we have studied the effects on the foetal weights of injecting pregnant rats with anterior pituitary extracts containing the diabetogenic-growth complex. The rat in such circumstances might reasonably be regarded as being in the "pre-diabetic state," although it must be pointed out that it is not possible to induce diabetes in this species by such injections (Young, 1938).

Experimental

Virgin adult female rats of mixed strains weighing 120–210 g. were used for the experiments recorded. They were put with bucks, and the finding of the "placental sign" (vaginal bleeding at about the 14th day of pregnancy) was adopted as a sign of conception. Subcutaneous injections were begun on the day of finding the placental sign and were given daily until the 20th day of pregnancy, when the animal was killed and the live foetuses were weighed. In each series of experiments control animals were treated similarly but were not injected. The fractionated anterior pituitary extract (fractionated A.P.E.) used was a "saline supernatant" fraction prepared by isoelectric precipitation from crude A.P.E. obtained from fresh ox anterior pituitary glands (Reid and Young, 1948; Reid, 1949). Two-thirds of the protein in this preparation consists of growth hormone, and it is possible that traces of other hormones present in the fraction are a constituent part of the diabetogenic-growth complex. The fractionated A.P.E. was unlikely to contain gonadotrophins in appreciable amounts, and tests carried out by three methods of assay failed to reveal their presence (Barns *et al.*, 1950).

Growth hormone (Armour and Co., J-21609R) was kindly supplied by the makers. Experiments were performed with this preparation to verify its activity, and the results clearly demonstrated its growth-promoting properties (Barns and Swyer, 1951). All the rats were weighed daily from the time of finding the placental sign. They were kept at 72° F. (22.2° C.), and were fed a vitamin-enriched cube diet *ad lib.*

Results

Controls.—Previous experiments (Barns *et al.*, 1950) had shown that saline injections and injections of liver extract had no effect on pregnancy in the rat; therefore no injections were given to the control animals. There were 35 pregnancies in the control group; seven of these were excluded from the series either because of early delivery or because of abnormality of the pregnancy such as uterine bleeding. Of the remaining 28 pregnant rats, 19 were killed on the 20th day of the pregnancy (corresponding with the fractionated A.P.E. experiment) and 9 on the 21st day of the pregnancy (corresponding with the growth-hormone experiment). From the former group of 19 controls there were 161 live foetuses and from the latter group 91. Further statistical details are shown in the table.

Fractionated A.P.E.—Eleven pregnant rats were injected with fractionated A.P.E. (0.5 ml. daily, corresponding in diabetogenic potency to 0.4 ml. of crude A.P.E. and to 1.2–2 mg. approximately of growth hormone); five of these rats were excluded from the series because some dead foetuses were found *in utero* when the animals were killed on the 20th day. The remaining six pregnancies produced 47 live foetuses. A further nine pregnant rats were injected with 0.3 ml. daily; two of these were excluded, one on account of early delivery and the other because of intra-uterine death. The remaining seven pregnancies produced 36 live foetuses. Because the total numbers were small it

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