

MELANOMA AND MELANOSIS

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by

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*Under her breast,
Worthy the pressing, lies a mole, right proud
Of that most delicate lodging.*

(*Cymbeline*, Act ii, Scene 3.)

THE TRADITIONAL APPROBATION accorded to the benign pigmented naevus, or mole, is strange. Areas of irregular pigmentation and angiomatous naevi are blemishes but the circumscribed mole, sinister potential progenitor of malign disease, is considered beautiful: not long ago the rites of feminine facial adornment included the application of one or more artificial moles. In those centuries when the Habsburg lip was to be seen at the centre of the European stage the black mole on the cheek of the Choiseul-Praslins was as proudly exhibited in the wings. Cutaneous moles are mentioned in the works of Marlowe and Dickens: reference is made to them in the *Comedy of Errors* and *A Midsummer Night's Dream*, while the plot of *Cymbeline* revolves around the focal point of Imogen's mole—"cinque-spotted like the crimson drops i' the bottom of a cowslip." Possibly the biblical Esau owed his hirsute appearance to an extensive hairy mole similar to that shown in Fig. 1.

The subject of pigmentation was one which clearly interested John Hunter. He wrote a paper entitled "On the Colour of the Pigmentum of the Eye in Different Animals," and his references to colour variations in skin and hair in both man and animals contain many shrewd observations.

Classification, histogenesis and diagnosis

The terminology of tumours of naevus-cell origin is confusing in that some use the term "melanoma" in reference to both benign and malignant types, while others restrict its use to the latter form. The use of the adjective malignant is undesirable at the bed-side and it is considered preferable to refer to the benign form as a mole or pigmented naevus and to the malignant as melanoma. This was common practice among former writers—Bland-Sutton, for example.

The essential feature of both benign and malignant varieties is that they arise from pigmentary dendritic cells known as melanoblasts. The origin of these cells is controversial and has been attributed to mesoblastic chromatophores (Sampson Handley, Ribbert); to the tissue elements

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forming the end-apparatus of cutaneous sensory nerves (Masson); to cells of epithelial origin exclusively (Willis, Post, Wieting, Favara); and to endothelial cells of the blood and lymph vessels.

Moles may be classified as intra-epidermal (naevus verrucosus); intradermal (cellular naevus, verucca mollis, soft wart); junctional (the type most prone to malignant change); and the blue naevus (of Jadassohn-Tieche, situated in the corium). Many pigmented naevi show histologically a combination of one or more of the above types. The Mongolian spot resembles the blue naevus: it is rare in Europe, occurs commonly over the sacral region, is often triangular and is blue-grey in colour. Though usually present at birth its appearance may be delayed for three or more years. Some persist to adult life; the majority have disappeared by puberty (Kahn).

Difficulty may arise in distinguishing moles and melanomas from other pigmented skin tumours. Chief among the latter are pigmented

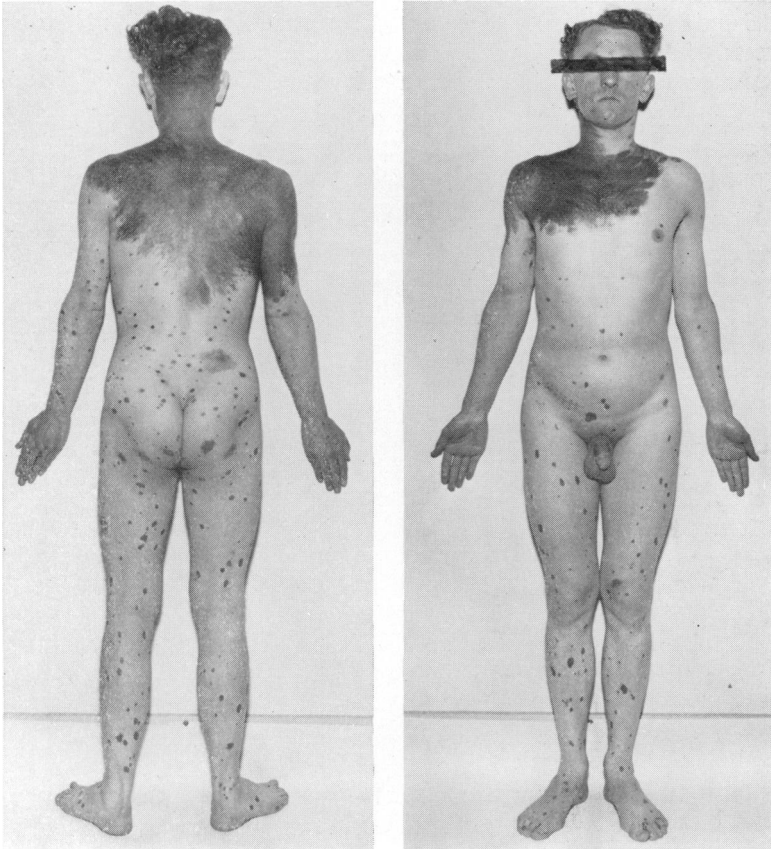


Fig. 1. Extensive hairy mole.

papillomas, pigmented basal-cell tumours and carcinoma in xeroderma pigmentosum. Womack has drawn attention to the suspicion which should be aroused by ulceration in the nail-bed, particularly in patients over the age of forty. Warts, ulcerating haemangiomas and pyogenic granulomas may simulate naevus-cell tumours: Ewing and Powell found that in 123 pigmented tumours of a size and nature to merit surgical excision ten were found on histological examination to be sclerosing angiomas (fibroma simplex, histiocytoma, dermatofibroma): in no instance had the diagnosis been made clinically.

In differentiating melanomas from pigmented naevi the most consistent sign is growth, either circumferentially or in the form of increased prominence of the tumour from the skin surface (Fig. 2). Other local features which have been seen in the present series of melanomas include alteration in colour, usually a darkening (though in two instances part of a mole became lighter in colour on transformation into melanoma): discharge from the surface of the lesion—this may be haemorrhagic, purulent or serous and may be no more than a slight encrustation (Fig. 3): increasing firmness of consistency or the presence of induration at the base: subjective sensations in the form of irritation or dull pain.

The excretion of melanogen, the colourless chromogen of melanin, may occur in cases of melanoma with metastases. The diagnostic and prognostic value of the sign has not been found valuable as the nature and extent of the disease is usually obvious by the time melanogenuria is present. Further, a few cases have been reported of melanogenuria in the absence of melanoma.

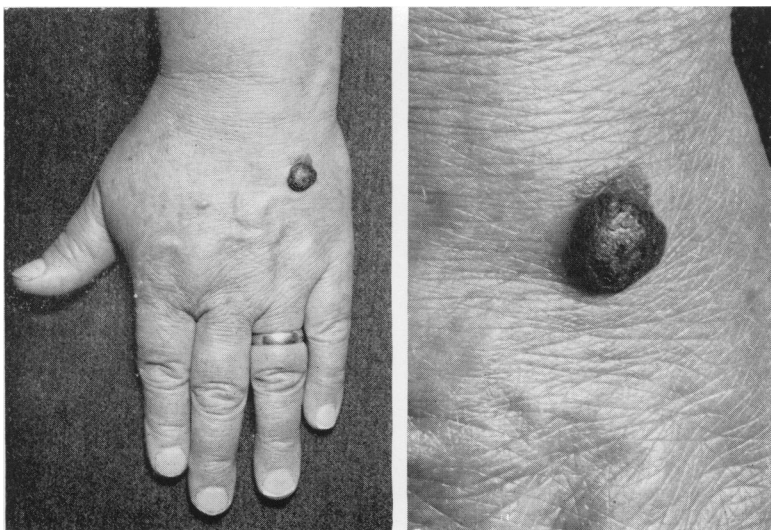


Fig. 2. Melanoma in a pre-existing mole showing proximal spread of pigmentation.

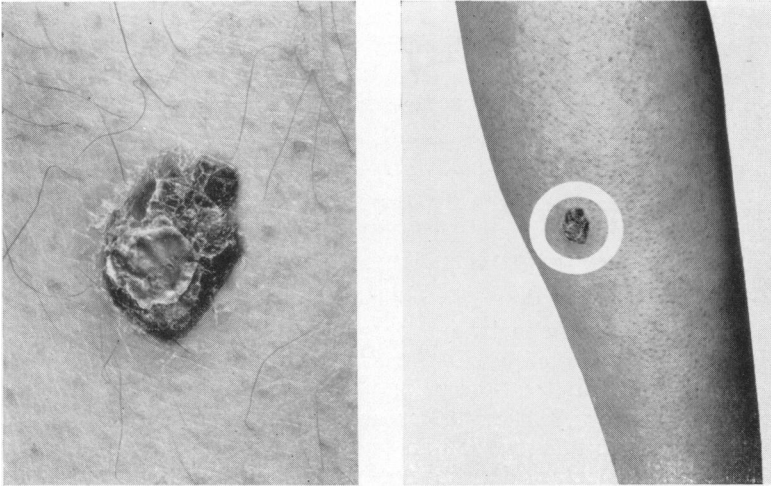


Fig. 3. Melanoma of calf showing encrustation.

The histological differentiation of benign and malignant forms of naevus-cell tumours is often difficult and the matter is complicated by finding typical features of melanoma in the pre-pubertal form of the tumour, which almost invariably is clinically benign. Spitz has found that pre-pubertal melanoma contains a larger number of giant cells than the adult form and regards the finding of giant cells in melanoma occurring in later age groups as evidence of relatively low-grade malignancy.

As mentioned above, the junctional naevus is the form of naevus-cell tumour most prone to become malignant and the presence of junctional cellular activity is the main criterion in estimating this change. Lund lists the following additional histological features of malignancy :

- (a) Excessively large, irregular scattered or otherwise bizarre masses or nests of cells at the dermoepidermal junction.
- (b) Deep penetration of large cells without differentiation to small cells or fibrillar forms.
- (c) An excess of mitotic figures.
- (d) Atypical and pleomorphic cells.
- (e) Invasion.
- (f) Trophic changes.
- (g) Inflammation, other than folliculitis, which is not accounted for by trauma.

Racial, sex and age incidence

Dark-skinned races are not immune from melanotic tumours. Muelling and Burdette collected 101 cases of melanoma from a hospital in New Orleans where admissions for negro and white male and female patients

are nearly equal ; 32 per cent. of the melanomas occurred in negroes. The degree of bodily pigmentation did not appear to be of significance. The presence of an antecedent mole was found less commonly in the negro. There was little evidence of racial difference in the incidence of antecedent trauma, the mode of spread, the effect of pregnancy or ultimate prognosis.

According to Lee the American negro shows a much smaller incidence of melanomas than the negro of Africa and he attributes this difference to the increased proportion of melanomas of the feet in the latter, who commonly wears no protective footwear.

The sex difference in melanoma is negligible. An analysis has been made of 1,406 collected cases (Pack and Livingston, Bickel, *et al.*, Butterworth and Klauder, Stewart, *et al.*, Hall, *et al.*, Daland (collected), Taussig and Torrey, Baxter, Driver and MacVicar, Wright, *et al.*, and the present series) : this revealed an exactly equal incidence in male and female. The pigmentary disturbances associated with pregnancy might be expected to give a preponderance to the female, but it may be that this is offset by increased susceptibility of the male to trauma of the body surface.

Melanoma occurs at all ages but is extremely rare before puberty. The juvenile or prepubertal melanoma almost invariably pursues a benign clinical course : nevertheless a few cases of juvenile melanoma which follow a malignant course have been reported (Coffey and Berkeley, Spitz, Webster, *et al.*, MacDonald). The age incidence in the present series is as follows :

Age	0-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Number of patients ..	0	8	6	11	15	15	4	1

Thus the maximum incidence is in the sixth and seventh decades : if the number of melanomas in each decade is correlated with the number of persons alive in that decade the increased tendency for melanoma to occur in the later years of life is pronounced. Bickel, Stewart, Raven and de Cholnoky in their respective series totalling 388 cases found the highest incidence in the sixth decade.

Body distribution of moles and melanomas

In order to assess the frequency with which moles occur and their regional distribution an enumeration was made in fifty male medical students and fifty females—medical students and nurses. Although the clinical identification of a pigmented lesion as being a mole is not always possible, the result agreed with the findings of Bloch and of Pack that each person has, on average, more than twenty moles upon the body surface. In each sex the average number on the upper half of the body

was more than double that of the lower, an observation made by other investigators.

Almost all members of the group underestimated the number of moles which were present : many were previously unaware of having any, a point of importance in attempting to elicit the proportion of pre-existing moles from the evidence of patients who come under medical care because of melanomas.

There was a tendency for moles to be numerous and small in dark-haired persons and few but larger in the fair-haired. In the included series of patients with melanoma was a female of thirty-seven years, having a melanoma of her right calf, who showed a total of 334 pigmented lesions, clinically identifiable as moles, upon her body surface.

No member of the student group had intra-oral pigmentation—a condition common in animals and seen amongst certain Asiatic and African peoples.

The regional distribution of melanomas and of moles show striking differences : moles are more frequent upon the upper extremities than the lower and yet melanomas are almost twice as common on the lower extremities as on the upper. Melanomas relatively often occur on the genitalia and the soles of the feet, sites where moles are seldom seen. This predilection for the lower parts of the body in the case of melanomas is unexplained : it resembles that found in synoviomas where, although the hands are the commonest site for the benign form, half the malignant types are found in the region of the knee and malignant change is uncommon in those of the hand.

More than 90 per cent. of melanomas are sited primarily in the skin and the eye (Fig. 4). Aggregation of pigment-forming cells are found in the central nervous system and Lence was able to collect forty-three cases of primary melanoma in this part of the body. There are many recorded cases of melanomas originating in mucous membrane, chiefly that of the rectum, mouth and genitalia. Rarely other primary sites have been reported and few parts of the body have escaped incrimination. It is frequently difficult to establish the primary nature in melanomas arising in bizarre sites and to be certain that such a tumour is not a metastasis from an overlooked or previously removed primary growth of the tegumen.

Attempts have been made to correlate the regional distribution of melanomas with the local concentration of melanocytes in the skin. Melanocyte frequency is usually assessed by using Bloch's dopa reagent together with the skin-splitting technique of Billingham and Medawar which causes the epidermis to separate from the corium by enzymatic action. The problem is whether the incidence of melanomas in various parts of the body surface is due to a difference in density of melanocytes or whether the melanocytes of some areas (*a*) possess an increased susceptibility to malignant transformation or (*b*) are more exposed to stimuli



Fig. 4. Melanoma of eye with secondary deposits of cheek.

capable of causing this change. Szabo found that the melanocyte count in the skin of arms and thigh was in the order of a thousand in each square millimetre : in the skin of face and forehead it may be two to four times as great. Much variation was found between the counts of melanocytes in corresponding skin areas of different persons. The number of such investigations is inadequate for conclusions to be drawn and it may

be that significant differences exist in the skin of any one part, for example, the medial and lateral aspects of the forearm. Melanomas show a tendency to occur more readily in heavily pigmented areas but such areas are for the most part exposed to the possible ill-effects of actinic rays and are not necessarily those with increased melanocyte densities. Sampson Handley has recorded an increased incidence of melanomas in Australia compared with that of countries where the sun has a less powerful influence.

Aetiology

There is no evidence that heredity plays a part in the production or dissemination of melanomas in man. Genetical studies have shown that hereditary influences are important in the production of melanotic tumours in platyfishes and in the fruitfly, *Drosophila melanogaster*. There is an hereditary factor in the melanomas of the anal region so commonly seen in grey horses.

Mention has already been made of the age and site distribution of these tumours. Other factors in the aetiology are the presence of a pre-existing mole, trauma and hormonal changes, especially those of pregnancy.

Laennec in 1806 noted a relationship between moles and melanomas. Some series indicating the incidence of a pre-existing mole in cases of melanoma are shown in the accompanying table :

Author	Percentage of patients with pre-existing moles	Number of cases
ACKERMAN	61	75
AFFLECK	83.5	317
DALAND AND HOLMES .. .	18	174
HALL, <i>et al.</i>	70.4	159
WEBSTER, <i>et al.</i>	65.4	104
PRESENT SERIES	65	60

It will be seen that with the exception of Daland and Holmes, the authors found at least 60 per cent. of their patients had pre-existing moles. Since most people are unaware of the number and site of naevi upon their bodies and since many are unsure of whether or not a mole was present at the site of a melanoma it is likely that any error in enumerating previous naevi is on the side of underestimation.

There is much evidence that injury is an important factor. The injurious agents are numerous : chronic irritation in the form of friction from shoes, suspenders, belts, braces, brassieres or collars : intermittent irritation resulting from shaving, combing of the hair, scratching or extraction of hairs, and trauma in attempting to eradicate moles by means of cautery, pastes, acids and corn plasters. Infection has a sinister reputation and would seem to play a specially important part in the subungual melanoma or melanotic whitlow of Hutchinson. De Cholnoky records the injudicious use of an electric needle in 4.3 per cent. of his cases and

Adair elicited a history of the use of this instrument in 10 per cent. of his 400 reported cases. Hewer reported forty-seven cases of melanoma in negroes of the Sudan in which three-quarters of the lesions were on the legs or soles of the feet: Sequeira and Vint recorded a series of fifteen melanomas in African negroes of which eleven were on the feet.

In the sixty cases of the present series a history of pre-existing mole was given in thirty-nine: in twenty, or just over half of these, there was an account of injury to the mole prior to the appearance of signs portending malignant change. Sampson Handley drew attention to an unusual feature of melanoma: that, while chronic irritation is well established in the aetiology of skin cancers, melanomas are exceptional in the frequency with which the tumour follows a single traumatic incident. In this series, of the twenty patients who gave a history of injury to a mole preceding the melanoma, ten attributed the change to a single noxious stimulus—a direct blow, attempted removal of the mole by the patient, a nettle-sting (Fig. 5), a contiguous boil or an area of herpes containing a mole which showed signs of malignant transformation as the herpes disappeared. A further four patients gave a history of the development of a black growth, later shown to be melanoma, following a single injury to a part where there was no evidence of antecedent pigmentary change. It is possible that a small mole may have been overlooked but, in all, the patient's statement was to the contrary. The phenomenon recalls Van den Brenk's account of a man who developed melanoma at both donor and recipient sites of an autogenous skin graft, in the absence of apparent



Fig. 5. Melanoma in pre-existing pigmented area following nettle-sting.

change in the skin of the donor area pre-operatively. Possible explanations are that trauma is the precipitating stimulus in an area where pre-malignant change has already taken place or that an unidentified biochemical state may temporarily exist in the body during which appropriate trauma at any site can give rise to a melanoma.

Most malignant neoplasms show an exacerbation of activity during pregnancy and in few is this more patent than in melanomas. The period of pregnancy is one of intense pigmentary activity as is seen in the increase of general bodily pigmentation, a deposition of pigment in the nipples and areolae, the appearance of naevi and often in the enlargement and darkening of those already present.

Scharnagel and Pack have reported a series of twenty-eight pregnant patients in whom either melanoma appeared in a pre-existing mole or else a melanoma which was previously present showed increased activity. In eight of these patients the mole itself had appeared during the pregnancy. The end result in the series was death of the patient in fourteen, or one half, within three years. In the present series three of the patients were pregnant: two died within five months. One of these aged twenty-seven years was seen in the eighth month of pregnancy. A melanoma of the left leg had been widely excised thirteen months previously. Enlarged left inguinal glands were present and a mass was palpable above Poupart's ligament on that side. Melanogenuria was present. Labour was induced and, owing to obstruction caused by tumour deposits in the pelvis, a Caesarian section was performed and a normal male child delivered. The patient died soon afterwards: the child, now aged six years, remains well. In spite of the widespread pelvic involvement no melanoma deposits were found on serial sections of the placenta. A number of examples of transplacental spread of melanoma have been reported: its absence in this patient in spite of the extent of melanoma in the pelvis is worthy of note.

A fuller consideration of the part played by hormones in the genesis of melanoma will be made later in assessing hormone therapy.

In four of the sixty patients in this series other forms of malignancy occurred at separate body sites before or after the appearance of the melanoma. These consisted of a squamous carcinoma of upper lip, a basal-celled carcinoma of outer canthus, a schirrous carcinoma of breast and a fibrosarcoma of elbow.

Mode of spread

The mode of spread in melanomas is clearly of the greatest importance. The subject may be considered from two standpoints, (*a*) the spread in the immediate environs of the primary growth and (*b*) the distant extension.

Whether in the early formative phase these neoplasms arise by cellular multiplication from a focus within a bed of normal tissue or by a general transformation of the tissues is controversial. Willis strongly supports the latter view and states "only after the formative field has all suffered

neoplastic change does the tumour grow solely by multiplication. The two processes, neoplastic transformation and proliferation, overlap, the former predominating during the early genesis of the tumour, the latter often being initially negligible but gradually taking increasing and finally exclusive part in the growth of the tumour." Dawson's classical work on melanomas showed that early cellular changes occurred not only in immediate apposition to the edge of the tumour but at a distance from it; isolated groups of cells undergoing malignant transformation were seen on serial examination of large adjacent tissue areas. It will, therefore, remain impossible to judge the extent of tissue removal needed to eradicate the primary melanotic growth until a means is found of assessing the area of the formative field. Further reference will be made to this later.

Distant spread is by the lymphatic and blood streams. In the dermis and subcutaneous tissue two lymphatic vessels generally accompany a small artery and vein. Sampson Handley has demonstrated that this contiguity can lead to invasion of the blood stream from the adjacent permeated lymphatics. He likened the arrangement of the lymphatics of the skin to numerous minute trees whose trunks descend to a network of roots, "here the analogy breaks down, for in the lymphatic system of the skin the trunks empty into a single large plexus, which may be visualised as formed by the free union and anastomosis of the roots of adjoining trees. It lies upon the deep fascia, is co-extensive with the surface of the body and is called the deep fascial plexus. This plexus is the main highway for the spread of lymphatic diseases affecting the parietal tissues." It was upon a conception such as this that Hogarth Pringle based the operation for skin melanomas which he described in 1908. His proposals were widely adopted: Grey Turner strongly supported the method.

The principles advocated were:

- (i) To surround the primary growth with an incision as far removed from it as is judged to be necessary.
- (ii) To run from the most convenient point in this generally elliptical or ovoid incision a second one along the normal course of the main lymphatic trunks as far as necessary to allow the free removal of at least the nearest lymphatic glands.
- (iii) To reflect the skin well back and to each side from these incisions, and excise the tumour with the whole of the deep subcutaneous tissue exposed containing the lymph vessels, the deep fascia of the limb and the fascia propria of muscles exposed along with the lymphatic glands in one continuous strip.

Pringle treated two patients in accordance with this method: the first a girl of seventeen presenting a melanoma at the flexure of the left elbow with axillary gland involvement, the second a man of thirty years with a melanoma of the inner aspect of the left thigh and infiltration of inguinal glands. In 1937 both patients were free from recurrence of the growth, thirty-eight and thirty years after operation. Latterly the advised

removal of the fascia propria has frequently been ignored and it is not uncommon to find a melanoma of the heel, for example, treated by excision of the neoplasm, the inguinal glands and a direct strip of intervening deep fascia. This presupposes a straight and superficial course of the lymph drainage in the limb which is in my opinion untenable. Many lymph vessels accompanying venous radicles and small arteries in the superficial tissues can be seen passing alongside these vessels and taking a course deep to the deep fascia to be incorporated in the perivascular tissue of the larger vascular trunks. In this the lymphatic drainage of the limbs resembles that of the head and neck. The early passage of a proportion of the lymph vessels in the limbs deep to the deep fascia is likely to be of greater practical significance in those melanomas which occur distal to the knee and elbow. It is standard teaching in textbooks of anatomy that the lymphatic vessels draining the superficial tissues of forearm and hand which pass across the medial side of the elbow pierce the deep fascia with the basilic vein ; and that in the lower limb the lymphatic drainage is partly to the deeply-lying popliteal glands and thence along the femoral vessels to the inguinal region. Thus, while melanomatous spread in the fascial plexus is accepted, the possibility of alternative extension in the deeper perivascular tissue must be admitted. It is interesting to note that in neither of Hogarth Pringle's patients was the melanoma distal to knee or elbow.

Some evidence in favour of this deep mode of spread has been collected. The lower limb of a patient of sixty-nine years, subjected to hind-quarter amputation for a melanoma on the medial side of the right sole with inguinal and external iliac gland enlargement, was carefully dissected, thirty tissue specimens being removed for histological study. Melanoma was found in skin specimens to a distance of three inches from the primary lesion and in the inguinal, external iliac and common iliac glands. In addition, melanoma deposits were found in perivascular tissue immediately below the origin of the posterior tibial artery. No malignant deposits were identified in the fascial plexus in twelve specimens taken from different positions between primary growth and groin. Deep spread was further exemplified in the case of a male of fifty-nine years who presented a melanoma of the right forearm with enlargement of a supra-trochlear gland and a single axillary gland. In dissection of the deep perivascular tissues between elbow and shoulder a minute dark nodule was identified and was shown on histological examination to be a melanomatous deposit. The findings in these two cases cast doubt upon the validity of accepted methods for the surgical eradication of melanoma.

Cessation of growth or spontaneous regression has been recorded in melanoma (Willis ; Daland and Holmes). Recently (1955) Allen reported an example of this spontaneous regression following pregnancy in a female of thirty-seven years. She was first seen in 1942, presenting a melanoma of the right forearm. This was excised and a melanomatous mass in the scar removed a year later. Ten and a half months after, in

the seventh month of pregnancy, the extent of widespread secondary tumour deposits justified a hopeless prognosis. In the third month of the puerperium all the nodules had disappeared with the exception of one in the right groin. Twelve years later she was entirely well.

Treatment of melanomas other than by surgery

Of the many non-surgical methods advocated for the treatment of melanomas irradiation has been the most used. It has been claimed that, while the great majority of melanomas are radio-resistant, a few are sensitive. In assessing this sensitivity care must be exercised in differentiating the true melanoma from other skin cancers, either squamous-cell or basal-cell, which happen to contain pigment. In my experience, irradiation is of very limited value in the therapy of melanoma: it may have been of some assistance in the post-operative control of the disease and has been of some help in the relief of pain in the advanced and inoperable case. Irradiation of the pituitary gland has not yet been shown to have influenced the course of the disease significantly.

In the past claims have been made for the use of colloidal lead phosphate and Coley's fluid in the treatment of melanoma.

The biochemistry of pigmentation processes has recently been the subject of much research and may have an important bearing in the aetiology and treatment of tumour formation in the specific cells concerned. The enzyme tyrosinase, identical with the "dopa-oxidase" of Bloch, facilitates the conversion of "dopa," or dihydroxy-phenylalanine, into melanin. Though this process occurs only to a small extent in normal skin it does so rapidly following exposure of the skin to ultra-violet light (Fitzpatrick, *et al.*). Aqueous extracts of human skin inhibit the formation of melanin and it is possible that this is due to the presence of -SH groups in the skin since iodoacetamide, which combines with the -SH groups, counteracts this inhibitory action.

Flesch and Rothman showed that the ability to inhibit melanin formation in the skin is directly related to the local concentration of -SH groups. Rabbits were partly shaved and the exposed skin subjected to high ultra-violet dosage. This resulted in a reduction of -SH groups to an amount of 20 per cent. of that previously present.

Tyrosinase is active only in the presence of traces of copper and it may be that in normal skin tyrosinase activity is inhibited by a combination of the -SH groups with the copper. In explanation of the increased pigmentation of Addison's disease it has been suggested that one of the functions of the normal adrenal is the maintenance of a high concentration of -SH groups in the skin and that defective adrenal function would result in decreased sulphhydryl content and hence increased tyrosinase activity and pigmentation. An older hypothesis (Bloch and Loffler) is that as both melanin and adrenaline are derived from "dopa" the suppression of adrenaline production in adrenal hypofunction releases more "dopa"

for conversion into melanin : more recently evidence has indicated an adrenal-pituitary relationship. Burn has noted that in Simmond's disease, where there is a deficiency of both pituitary and adrenal function, pigmentation is most uncommon. Daily injections of 0.5 mg. melanocyte-stimulating hormone (MSH), which is formed in the intermediate lobe of the pituitary, cause darkening of human skin and pigmented naevi (Lerner, *et al.*). Hydrocortisone inhibits the release of MSH from the pituitary while noradrenaline and adrenaline inhibit the action of MSH upon the melanocytes. Decreased production of hydrocortisone results in increased release of MSH and ACTH by the pituitary. It was found that in the later months of pregnancy more MSH was produced in spite of a high hydrocortisone level and this may account for the increased pigmentation seen during this time.

Other hormones play a part in pigmentary processes : oestrogens induce pigmentation and when applied locally cause pigmentation at the site of application. Androgens act similarly (Edwards, *et al.*). In men who are castrated exposure to ultra-violet light produces little pigmentation, but even after the lapse of some days the administration of testosterone propionate has been followed by pigmentation of the areas previously exposed.

Melanogenesis may be influenced by other local applications : hydroquinones, used in industry, have caused areas of leucoderma at the site of contact and use has been made of this action in the treatment of areas of pigmentation with considerable success (Denton, *et al.*).

Dermal or junctional naevi show negative or weakly positive tyrosinase activity while melanomas give a strongly positive reaction : other types of skin cancer fail to show any reaction. It therefore seems that an active tyrosinase system is associated with the malignant character of the human melanocyte and that in the benign pigment-cell the system is less active or inhibited. The difficulty lies in establishing a relationship between increased pigmentary activity and the growth of melanoma : whether increase of pigmentation is an incidental sequel of such growth or whether the stimulus to pigmentation is also an influence in the appearance, the rate of growth or the rapidity of dissemination in melanoma. If the latter is true then control of pigmentation should form a means of therapy in melanoma.

The use of tyrosine labelled with radio-active carbon is being developed for the examination of tyrosine activity, radio-active melanin being formed. This type of investigation may establish a means of testing the actual potential malignancy in melanocytic tumours and in the identification of malignant transformation in a mole. The investigation of inhibitor agents may prove of great importance. Monobenzyl ether of quinone, which inhibits the formation of melanin in human skin, has been used by Kelly in melanomas but was found to be ineffective. Possibly physical agents such as ultra-violet rays, X-rays and even inflammatory

processes cause the oxidation of the -SH groups and hence relax the inhibitory influences and release the enzymes. The sulphhydryl content of skin taken at varying distances from a primary melanoma has been estimated in an attempt to provide a biochemical means of identifying the extent of a "pre-melanotic field" around the primary lesion. It is possible that correction of biochemical abnormality in the scar resulting from excision of a melanoma and in the adjacent skin may reduce or abolish the risk of secondary melanotic nodules developing in the area. These investigations are, as yet, incomplete.

The surgical treatment of melanoblastic tumours

The following are considered points of importance in the surgical treatment.

Any mole which gives rise to suspicion of malignant transformation and any mole which is subjected to repeated trauma should be excised.

No form of partial removal is allowable in melanoma and the tumour should be excised with a wide margin of surrounding tissue, the depth of the excision extending to include the fascia propria of underlying muscles. The width of the surrounding tissue which need be excised is not ascertainable at present. The appearance of further melanoma deposits near the site of removal of a primary tumour does not necessarily indicate inadequate removal of the latter but may be additional growth in a pre-melanotic field where, possibly, the trauma of operation has acted as a stimulus to malignant growth (Fig. 6). In the limbs and trunk sacrifice of a large area of surrounding tissue is justifiable, the defect being closed

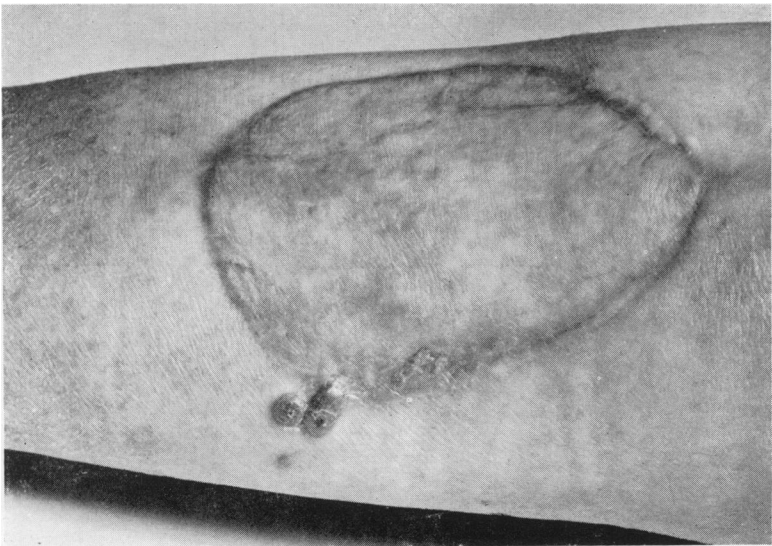


Fig. 6. Secondary melanoma deposits in leg. Previous excision of primary growth and skin-grafting.

by skin-grafting if necessary. At other sites—the face, for instance—careful thought is required to balance the opposing factors of adequate excision and needless mutilation. In all cases the excised tissue is examined at the circumference and deep aspect to ensure that removal of the primary melanoma is complete.

If the course of the lymphatic channels is predictable, as in a melanoma near groin or axilla, the excision should be extended to include the related glands and intervening tissue together with the perivascular lymphatics in one block. Melanomas situated at a distance from the related glands should be treated by removal of the primary tumour and excision of the glands, even if these are not obviously affected on clinical examination. Occasionally, as in melanomas in the mid-line of trunk, head and neck, it may not be possible to determine which group of glands are likely to receive the main afferent stream. In such cases it is advisable to confine surgery to the excision of the primary lesion, and thereafter to examine the patient frequently, performing a block dissection of any glands which may show signs of infiltration. The removal of long strips of deep fascia between primary growth and related glands is of doubtful value and cannot be regarded as a means of eradicating the disease.

Digital and subungual melanomas should be treated by amputation of the digit at the metacarpo-phalangeal or metatarso-phalangeal joint with block dissection of the axillary or inguinal glands (Fig. 7). More conservative attempts in removing the primary tumour is likely to result in local recurrence (Fig. 8).

Melanomas in the forepart of the foot, the toes excepted, are best treated by a Syme or a Pirogoff amputation. Melanomas in the proximal part of the foot and the heel require amputation at the site of election in the lower leg with block dissection of the inguinal glands.

In the oral cavity melanomas are treated according to the principles already enunciated: the fitting of a prosthesis may be necessary. Those which occur in the anal canal are usually highly malignant and require most radical treatment.

Prepubertal melanomas should be excised but removal of the related glands is not performed unless they are clinically involved, since metastasis is exceptional.

Early in pregnancy moles which are subjected to friction or other trauma should be excised. The treatment of melanoma in the pregnant patient is of the utmost urgency and should include termination of the pregnancy. Sterilization is not indicated since patients who have had melanomas adequately excised and have remained free of further growth for several years have passed through subsequent pregnancies without trouble.

In spite of the poor prognosis in cases presenting glandular involvement pre-operatively there have been a number of recorded cases where apparently inevitable early death has not followed and therefore hesitation

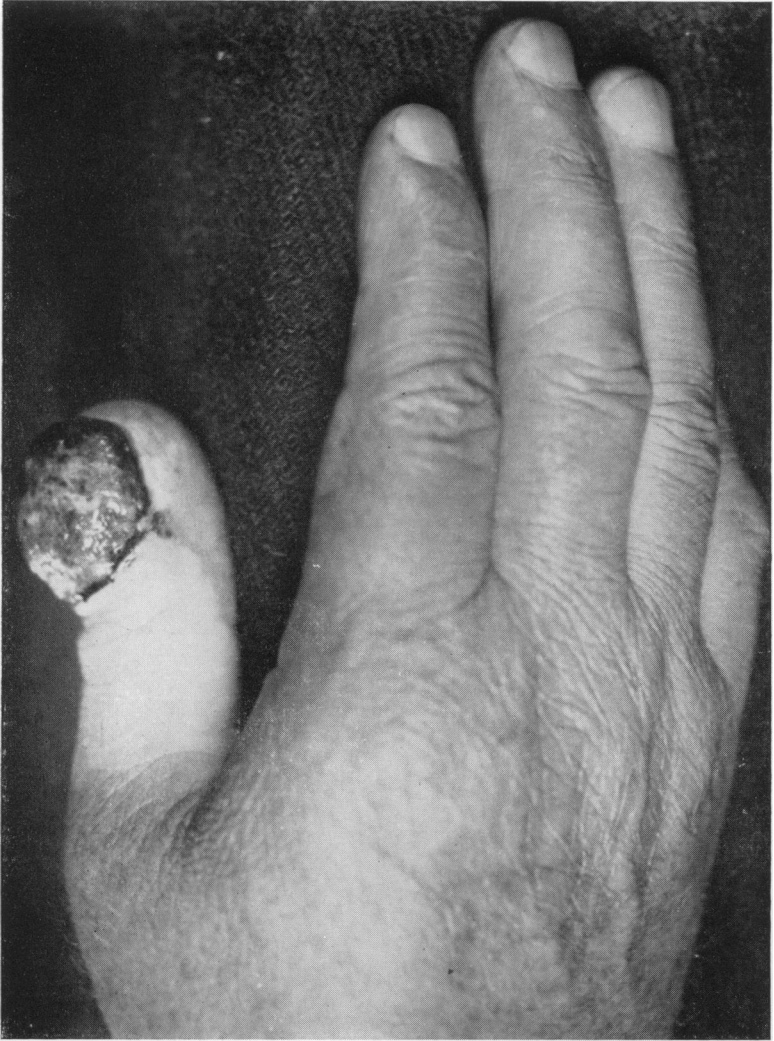


Fig. 7. Melanoma of thumb.

should be exercised in labelling a growth as inoperable in the absence of general metastases. Palliative surgery has a place in the removal of fungating tumours in the presence of general metastases: occasionally peripheral nerve section or chordotomy is indicated for terminal pain (Fig. 9).

In melanomatosis castration, adrenalectomy or hypophysectomy have not as yet been proved of value.

Where inguinal glands are found pre-operatively or at operation to be affected it is necessary to extend the excision to include the iliac glands. In the present series access to these glands has been obtained by division of the inguinal ligament in the line of the femoral artery : this has not given rise to post-operative weakness in the area. Fore- or hind-quarter amputation is indicated where more conservative measures in the affected limb are likely to be ineffective : two such cases are included in the present series—one died within four months of operation of generalised metastases, the other is alive and free from recurrence three years after hind-quarter section.

Prognosis

The prognosis in melanoma, in spite of some improvement in recent years, compares unfavourably with that of other forms of surface cancer. Delayed or inappropriate treatment are major adverse factors : in the present series the average time between the appearance of signs suggesting malignant neoplasia and the seeking of medical advice was over six months. Adair, in a series of 400 cases, found the time between the onset of lawless growth and the start of treatment averaged two years and two months.

The prognosis is related to the stage of growth ; the best results are in lesions clinically benign and found, on histological study after excision, to be malignant. Next are those melanomas in which the only sign of

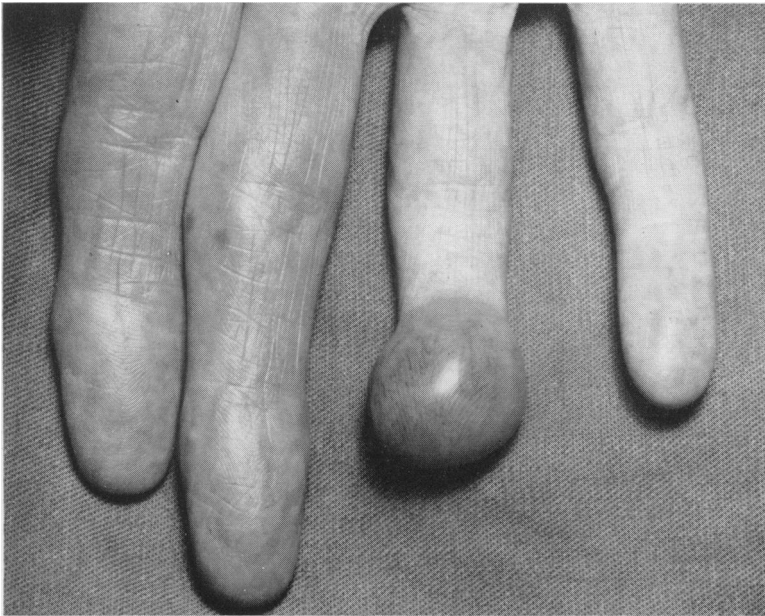


Fig. 8. Melanoma of finger-tip. Recurrence following inadequate removal of primary tumour.



Fig. 9. Secondary melanoma in left groin and lower abdomen. Dorsal chordotomy performed for the relief of pain (by Mr. C. Langmaid).

malignancy is enlargement or darkening of a pre-existing mole. The outlook worsens if bleeding or infection is a feature: it is still worse if there are pigmented deposits adjacent to the primary lesion or if the regional lymph nodes are infiltrated. General metastasis is followed by early death although, as noted earlier, a few instances of complete remission have been recorded in the gravest of cases.

Before puberty there is likely to be no reduction in the expectation of life for patients treated for melanoma: a precipitous drop in survival rate occurs in patients afflicted after puberty. The rapid dissemination which frequently occurs in pregnancy is well-known.

Melanomas of the genitals, of mucous membrane and of hands and feet have a worse prognosis than those at other sites. Pack regards the

ungual types as favourable with a tendency to metastasise late: two of the three ungual melanomas in the present series conformed to this pattern, the third metastasised most rapidly of all.

Reported five-year survival rates vary from nil to 50 per cent. An analysis of 680 collected cases showed a rate of 18 per cent. of five-year survivals; these patients were from centres where the treatment of melanomas was of special interest and it is probable that the overall survival figures would be lower. Five-year arrest does not indicate immunity from later extension of the melanoma and the ten-year survival has been shown to be half that of the five-year rate.

Melanosis

Excessive pigment in the skin—melanosis or melanism—is a rare condition. Albinism, the absence of pigment in the skin, is more common and is found in all types of animal, vertebrate or invertebrate. Those animals which lack pigment in the skin lack it in the uveal tract also.

An abnormal distribution of pigment in the skin of man may be associated with disease elsewhere in the body. Melanosis unassociated with disease occurs in man in a congenital or an acquired manner. The former, when extensive, is piebaldism and shows a tendency towards bilateral symmetry. A classical example was Mary Sabina whose portrait is hung in the Royal College of Surgeons. Last year I accepted an opportunity of examining a human piebald, a female of forty-four years from Tamatave, Madagascar (Fig. 10). Her history was that her parents were not closely related and did not show pigmentary abnormality: both were negro. Of the fifteen children, five of nine girls and three of six boys were piebald: of these some had married. None of the normally-coloured produced piebald children: some children of those who were piebald were also piebald, others not. Apart from the darkening of pigmented areas in the first few weeks after birth the pigment pattern remained unchanged. In all piebald members of this family the pigment deficiency was greater anteriorly than posteriorly and there was a conformity of pattern in this deficiency in scalp, forehead, neck and trunk. In the lower part of the face and the limbs the pattern was irregular and differed much between the various members of the family. It is tempting to suggest that the basic defect is an arrest in the passage forwards from the neural crest of pigment-forming tissue.

Exposure of skin which is normally covered and unpigmented results in pigmentation. Thus in the uncircumcised negro the skin of the glans penis is unpigmented, but after circumcision it becomes as dark as the rest of the skin: a similar change is seen in the vaginal portion of the cervix uteri in the negress after complete uterine prolapse (Shattock).

Some amphibians and fish possess the ability to modify their colour in response to nervous stimuli. In these animals superficial branching (Deiter's) cells are filled with melanin granules. On exposure to light the

protoplasmic processes retract and the pigment is concentrated in the cell body, this change resulting in an apparent lightening of the body colour. In octopus there is a modification of pigment function whereby the animal is enabled to store black pigment in an ink-sac and eject it in large quantities when irritated.

It is interesting to note in this connexion that certain blind cave fishes (*Anoptichthys hubbsi*) acquire melanophores after exposure to light for some months. These melanophores are found not only in the skin but also in the meninges and in the peritoneum. The genesis of the cells is not in response to stimuli by any normal optic mechanism since the fish have no retina or lens and many also lack an optic nerve (Rasquin).

Pigment behaviour in chick grafting experiments

The control of feather colour pattern in melanophore grafting in different breeds of embryo fowls has been studied by Willier and Rawles. The influence of the subjacent mesoderm and of the humeral agents of



Fig. 10. Female aged 44 years showing the typical pigment pattern of piebaldism.

the host was studied following the grafting of donor skin ectoderm from the head to the wing region. When such grafts are made, usually at the base of the wing-bud, the down which grows is replaced, after hatching, by juvenile feathers which have the shape, the rate of growth and tract distribution characteristics of feathers occurring in corresponding regions of control host chicks but invariably with the colour or colour pattern of the donor breed.

The discovery of melanin granules of a shape, size, and colour peculiar to the donor in the barb and barbule cells of the host feather is evidence that donor melanophores have entered the epidermis of the host feather germ.

Following the origin of the melanophores further, the next problem is the tissue source whence they migrate to the donor graft. Reviewing the evidence in favour of an extra-epidermal origin and lateral migration of melanophores from the neural tube region Dorris concluded that the neural crest in the chick embryo is the source of the melanophores. She tested the capacity of the neural crest region in the chick to produce melanophores and was able to show that when the neural crest is grafted to a host embryo it has the ability to produce donor-coloured down areas.

In an attempt to show that the neural crest has the exclusive property of being able to produce epidermal melanophores Ris transplanted chick tissue from various levels and concluded from subsequent examination of the graft areas that a definite correlation exists between the capacity of a graft to produce pigment and the morphological development of the neural crest: only those grafts known to contain neural crest, the region from which it arises or its migrating cells are able to produce melanophores. More recently this pigment-producing capacity has been traced a stage further, to presomite blastoderm, precursor of the neural crest.

The factors which are responsible for the degree and direction of melanophore spread in the host tissue are as yet unidentified, but it is known that the migration follows certain general directions, not normally crossing the midline either ventrally or dorsally.

Humoral agents such as thyroxine and the sex hormones may play a part in determining the pigment pattern in adult plumage (Danforth, Lillie and John). The degree to which these substances may modify pigmentary processes is as yet undetermined.

Genetic Influences in Pigmentation

During the course of this century geneticists have advanced far in the study of pigmentary processes and the development of pigmented tumours. Much of the basic information on aspects of genetics such as gene segregation, linkage and sex-linked characteristics was derived from earlier research into the physiological properties of pigment. A large part of

genetical interest has been focused upon the fruit fly and the platyfish hybrids, since both organisms lend themselves readily to genetical and cytological analysis.

At least twenty-four different strains of the fruit fly (*Drosophila melanogaster*) have been shown to develop tumours. In a few the growth probably represents a degenerative rather than a neoplastic change. The majority of the remainder have tumours which are melanotic. Though only present in a proportion of the insects, the susceptibility to such growths is transmitted by all. It has been possible not only to identify the chromosomes responsible for tumour susceptibility but also, in certain instances, to determine the position of the responsible genes on a specific part of each chromosome.

Burdette has used *Drosophila* to investigate carcinogens and the ability of certain chemical agents to cause mutations. These studies lend support to the view that mutations are likely to play a prominent rôle in the aetiology of tumours. Nitrogen mustard was found to be a potent source of mutation production: methylcholanthrene gave rise to a negligible number of such changes.

Classical experiments were made upon the platyfish (*Platyocilus maculatus*) which frequents the Atlantic coast rivers of Mexico, Guatemala and British Honduras, by Myron Gordon. Six natural groups are known. In 10,000 specimens of platyfishes and swordtails examined no melanotic tumours were discovered. But, under laboratory conditions, when a spotted member of one natural group was mated to that of another, tumours developed in their spotted hybrids. In each type of mating, either intergeneric, interspecific, or intraspecific, the fishes represent different genetic groups and their hybrid offspring develop melanomas or melanosis in response to a genetic imbalance. This imbalance is thought to be between the genes for the macromelanophores—five of which have been identified—and their growth regulators, specific macromelanophore modifying genes.

Myron Gordon attempts to explain these findings in the following way. When two groups of individuals become separated, as by a geological accident, each group will, in time, become genetically distinct. The differentiation depends upon the accumulation of random mutations and its degree upon the time of separation and other factors as environment, rate of growth and frequency of the breeding cycle. These mutations have to withstand the challenge of natural selection and if successful so change the organism that in the process of time the differences between the groups become so great as to warrant the identification of a new species. It would seem probable that in the early part of their existence all platyfishes were uniformly coloured and the aggregation of pigment into spots or macromelanophores happened as a mutation. However lethal the macromelanophore mutation may have been some platyfishes were able to overcome the challenge and adapt themselves to the change.

When a genetically balanced spotted platyfish of one group is mated to a normal member of another group which has been separated from it for many centuries the latter is imbalanced genetically towards the macro-melanophore genes and the effect of this is shown by atypical pigment cell growth in the spotted hybrid offspring.

In the study of genetic influences it is of great importance to differentiate with care influences concerned with abnormal pigment cell behaviour from those related to the development of melanotic growths. Nevertheless, the work upon platyfishes lends some support to a suggestion that there is some affinity between the two processes: that the relationship is that of degree in gene difference between one group and another, the greater the disparity the more likely are melanotic tumours in the offspring rather than mere benign pigmentary abnormalities.

Melanomas in animals

Melanomas have been found in many types of vertebrates: amongst domestic animals they are commonly seen in the ox, the horse and the dog, less often in the cat, the sheep and the pig.

The occurrence of melanomas in horses has several unusual features worthy of comment. It has been estimated that about 80 per cent. of grey horses of either sex develop one or more melanomas if they reach old age. There is no such predisposition in horses of any other colour although none is immune. The site at which melanomas most frequently appear is the skin of the inferior side of the tail near the anus. In appearance they are often mushroom-like excrescences and have been known to weigh as much as sixty pounds. Although the maximal incidence is in this area there is a predilection for any deeply pigmented, hairless region and the tumours are comparatively common in the genital region, the mammae, the scrotum and the margin of the lower lip (Spencer).

The glands nearest to the site of the primary tumour are involved early. From origins in the ano-genital area spread is first to the inguinal glands and these seldom break down and ulcerate at the surface. Wasting is not usually present and the animal remains fit for work. Extensive deposits may occur in the retroperitoneal tissues, the spleen and at the root of the lung. Infiltration is not a notable feature and physiological disturbance is more often due to mechanical displacement of the viscera according to the extent and size of the secondary deposits. Spencer noted the tendency for these growths in the horse to become cystic, a characteristic infrequently seen in the human. Though this slow and relatively benign course is usual, highly malignant forms are seen occasionally.

Recently I had an opportunity of examining fourteen grey circus horses of varying age and breed. In two of the older horses melanomas were present at the ventral part of the root of the tail. I was informed that such a finding was common, that the lesions were known as "knots," and that in some farming communities total amputation of the tail in

affected horses was performed in the belief that life and capacity for work were thereby prolonged.

Equine melanomatosis has been studied at length by McFadyean, who was unable to suggest any external cause in the nature of diet, work or environment which might affect the grey horse particularly. He observed that in black, bay or brown horses the demand for new melanin arising from the annual casting of hair is subject to little variation throughout life: in grey horses, however, practically from birth the demand for melanin diminishes and after middle life rapidly decreases owing to the growing preponderance of white hairs which are free of pigment. Since the process is not that of bleaching there must be in the grey horse, as opposed to those of any other colour, considerable disturbance of pigment metabolism, especially in the later years. It is perhaps significant that the site of predilection for melanoma is the deeply pigmented region beneath the tail where the long hairs are based and where the decline in demand for melanin is maximal.

One further observation worthy of note is that no significant sex difference in the incidence of melanoma in grey horses has been found. Since the great majority of males are gelded early in life it is unlikely that hormones originating in the sex glands play any part in the causation of the tumours. The possible importance of sex hormones in melanomatosis of the human subject has been elaborated previously.

Trauma does not seem to play a part in the aetiology of melanoma of domestic animals. The harness tail-strap might be invoked as a source of recurrent friction in the carthorse but the area below the tail is also the common site in bovines. Relatively the udder of the cow is also frequently affected: in the dog many melanomas are found in the digital regions and in the scrotum.

Nearly all melanomas in the animals are found in the skin: it is rare to find primary involvement of the uveal tract.

Melanosis coli

Melanosis coli is a condition in which there is deep pigmentation of the mucous membrane of the colon due to the deposition of melanin in the tunica propria layer of the mucosa. Cruveilier (1830) has been accredited with the first reference to the condition. The name "melanosis coli" was first applied by Virchow in 1858. "Colitis pigmentosa," a term later given, has since been discarded as associated inflammatory changes have not been demonstrated. Pick, in 1911, collected twelve recorded cases and added six from his own practice. Subsequently many accounts have appeared in the literature, the first large series diagnosed by sigmoidoscopy being that of Bockus, Willard and Bank in 1933.

The extent and site of colonic involvement is variable. Pick described involvement of the entire colon and commented upon the abrupt cessation

of pigment at the ileocaecal valve. Usually the depth of pigmentation is maximal in the caecal region, diminishing progressively thereafter: rarely the reverse is found, the rectum showing the darkest colour. The pigment may be distributed in a patchy manner. Involvement of the vermiform appendix is common and occurs with or without similar changes in the remainder of the large intestine. Similar pigmentation has also been described in the ileum and in the lymph glands of the mesocolon.

Melanosis coli is frequently found in association with carcinoma of the colon. In forty-three cases of carcinoma coli over the age of forty years, Stewart and Hickman demonstrated melanosis at autopsy in twenty-one (48.8 per cent.).

For comparative purposes 284 non-cancerous cases of the age of forty years were examined post mortem and melanosis coli was found in thirty-seven (13 per cent.). The higher incidence of melanotic pigmentation in carcinoma of the colon was attributed to concomitant intestinal stasis. The discolouration was usually more striking proximal to the growth than distally. Porter in 1926 described a case of carcinoma of the terminal ileum in which there was melanosis of the caecum. Bland-Sutton recorded a case in which a carcinoma of the colon was seen to grow from a melanotic area: subsequent examination failed to demonstrate the presence of any pigment in the carcinomatous tissue. Thus, while carcinoma of the colon may indirectly by reason of the associated stasis be a cause of melanosis coli there is no evidence that the latter condition in any way contributes to the development of cancer and its presence is of no sinister significance.

Histological examination of large intestine affected by melanotic pigmentation shows that the surface epithelial cells are devoid of pigment: the granules are mostly contained in the large mononuclear cells of the mucosal stroma or tunica propria. In addition free pigment may be seen outside the cells locally in lymphatic structures: invasion of the muscularis by a few pigment-containing cells has been reported.

Many attempts have been made to trace the origin of the pigment in the tissues of the colon. The ingestion of heavy metals, either mercury or lead, was invoked as the cause by early writers but chemical analysis by Pick and Solger failed to confirm their presence. A haematogenous origin of the pigment was suggested by Virchow but again this has not been substantiated. Some doubt exists concerning the nature of the pigment; whether it is identical with the true melanin which occurs in ectodermal tissues. On finding slight differences of a chemical nature some observers have concluded that the pigment of melanosis coli should be regarded as intermediate between true melanin and the dark "wear and tear" pigment found in all tissues.

Pick put forward the view that in some persons an oxidative ferment was produced by the mucosal connective tissue cells and that the pigment was produced by the action of these ferments upon aromatic protein

decomposition substances such as indole and skatole. Dalldorf suggested that the pigment could be accounted for by bacterial action within the bowel lumen, absorption being then effected by the mucosa. Laidlow failed to demonstrate colonic cells in melanosis coli capable of producing melanin and believes the pigment is derived from ingested foodstuffs and withdrawn from the gut by phagocytosis.

Melanosis coli is not confined to the white races and may occur at any age : it is predominantly a condition of the decades between thirty and sixty years, the time at which constipation is commoner. It is seen more frequently in females than in males. Bockus and his associates demonstrated melanosis in twenty-five (4.7 per cent.) patients out of 532 submitted to sigmoidoscopy : chronic constipation was present in all cases shown to have melanotic change. Almost invariably the degree of pigmentation is most intense immediately within the anal sphincter.

Though the incidence of chronic constipation in melanosis coli is high it is not possible to incriminate any dietary fault nor does it appear that putrefaction changes are higher than in cases of colonic stasis without melanosis.

Barium enema study was performed in twenty-seven cases of melanosis coli by Bockus, Willard and Bank and in twenty-three long, redundant colons were found. Spastic changes were strikingly infrequent, the tendency being towards distension.

The association between bowel dysfunction and melanosis coli has long been recognised : Hurst believed that a causative factor was the diarrhoea produced by laxatives of any kind for constipation or the fear of constipation resulting in excessive putrefactive changes. Earlier, in 1928, Bartle described pigmentation of the colon in patients taking cascara for long periods. Since the taking of laxatives is so widespread the establishment of any definite relationship with melanosis is fraught with difficulty. There is, however, some evidence that the group of cathartics which includes cascara, aloes, rhubarb and senna and which owe their laxative quality to the presence of irritant anthracene or emodin compounds show a significantly high rate of usage by patients with melanosis coli.

In all cases of melanosis coli reported by Bockus and his co-workers there was a dependence upon laxatives for bowel evacuation. In thirty-five of the patients it was possible to ascertain the laxative used and in all but eight this proved to be cascara, alone or with Alophen, aloin or rhubarb. Five of the remaining eight used Alophen : the great majority of the patients had taken these laxatives for at least a year. They found that fewer patients suffering from melanosis coli have appeared since anthracene purgatives have become less popular. Further, fewer cases of pigmentation associated with cancer of the colon are now seen if the proportion of cases recorded by former writers is compared with those of recent date.

Melanosis coli is of immanent character. Many patients who have been shown to have the condition on sigmoidoscopy have, on correction of their colonic stasis and the avoidance of anthracene-containing laxatives, subsequently been observed to become free of pigmentation (Bockus). The usual period which elapsed before the complete disappearance of melanositis within the visible field of the sigmoidoscope was between four and twelve months.

Whatever the cause of the colonic pigmentation its presence has not been known to give rise to any adverse symptoms and since it has been exonerated from the list of possible aetiological factors in carcinoma it is now a subject of academic interest rather than of any clinical significance.

Melanin pigmentation in disease

Excessive melanin pigmentation occurs in association with many diseases affecting man. Addison's disease is a common example and its pigmentary manifestations are not surprising in view of the chemical affinity between adrenaline and melanin. Buccal pigmentation may be present, a condition sometimes also found in pernicious anaemia and excessive arsenic intake.

Acanthosis nigricans is rare: it is associated with carcinoma of the stomach and the pigmentation, usually of neck or trunk, resembles a powdering of the part with coal dust.

Chloasma is a sequel or accompaniment of abnormal conditions of the abdominal viscera, especially those uterine in origin and also of cachexia and various cutaneous eruptions. Pigmentation is sometimes seen in rheumatoid arthritis, Hodgkin's disease, leukaemia, abdominal tuberculosis, chronic constipation, syphilis and, not unexpectedly, in neurofibromatosis.

Recently a further connexion between abdominal abnormality and pigmentation has been established in the syndrome of Peutz-Jeghers: here intestinal polyposis is associated with pigmentation, dark brown or black specks which are most frequently found on the face, especially the external nares, and on the fingers and toes. Mucous membrane of lips, cheeks, gums and palate may be similarly affected. The disease is hereditary and familial. The patient, usually a young adult, presents because of symptoms relating to the intestinal polyposis—often abdominal pain, episodes of intestinal obstruction, vomiting or rectal bleeding. Melanin pigmentation is thus an accompaniment of many widely differing diseases. Apart from the predilection for the disease to be of an intra-abdominal nature, no common factor is evident.

The many observations upon the behaviour of melanin pigmentation, in health and disease, appear largely dissociated and the most promising line of future investigation will be in attempting to correlate further these observations. Therein lies the answer to many of the problems in the complex subject of melanomas and melanositis.

C. W. D. LEWIS

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OVERSEAS VISITORS TO THE COLLEGE

ON WEDNESDAY, 1st August, the President received a visit from Professor Ougrumow of the Institute of Traumatology and Orthopaedics, Moscow, and Professor Goloudnow, Neurosurgeon at Leningrad.