The Bradshaw Lecture

ON

MELANOSIS

(MELANIN: MELANOMA: MELANOTIC CANCER).

DELIVERED BEFORE

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BY

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(With Special Plate.)

THE subject of this lecture, Melanosis, in some of its aspects has engaged the attention of former lecturers and of contributors to the Museum of the College.

I propose to relate briefly some recent observations from which there has been obtained an increase of knowledge as well as indications of the lines along which further research is desirable.

Some races of mankind have developed a pigment, melanin, which together with a free secretion from the skin serves to protect the central nervous system against the effects of excess of sunlight, and enables such races to work under the sun in the tropics, because the pigment prevents injury from the ultra-violet light rays. Races inhabiting colder regions, with much less pigment in the skin, have scattered collections of pigmented cells—melanomas. These have the characteristics of "congenital rests," which, although they show no outward change, yet as life goes on undergo an insidious degeneration. Without any sharp line of demarcation the degeneration may pass to the formation of a new growth—melanotic cancer.

Subject to individual differences this malignant change tends to arise in the later periods of life. In horses which turn white with age melanotic cancer supervenes with increasing frequency the longer the animal lives. In man melanotic cancer is a relatively rare form, but it has the peculiarity that two factors are associated—a proliferation of cells and a multiplication of the melanin pigment. The degeneration of the "congenital rest" into melanotic cancer cannot be prevented, nor the further course of the disease controlled. Once the malignant change has started, even although there is no clinical manifestation of it, a metastasis sets in forthwith. The secondary growths, however, displace rather than infiltrate, so that the metastasis may not become apparent for a long while. In addition to those on the surface there are collections of pigmented cells scattered in deeper structures which may be likewise regarded as "congenital rests." Through various causes, moreover, pigmented patches may be acquired which also may tend to undergo malignant degeneration.

Recent chemical observations have overcome to a large extent the difficulties concerning the analysis of melanin. A colourless melanogen by oxidation becomes a coloured melanin and is closely allied in composition to adrenaline. Both are connected with other protein derivatives which have the same feature—that of changing into coloured substances as the result of oxidation. Used as histological stains some of these serve to demonstrate the presence of melanogen in epithelial cells by converting it into melanin. Again, substances contained in coal tar, allied to those derived from proteins, when introduced into animals cause melanin to form, as well as giving rise to cancer.

Concerning the history of melanosis I limit myself to noting some of the contributors to the Museum and former lecturers.

Hunter examined the skin of a negro by macerating it, and found that it separated into three layers—corneous, mucous, and fibrous; the pigment was situated in the mucous layer, which rapidly liquefied and the pigment then collected as a sediment. The skin on the dorsum of the negro's foot was deeply pigmented, that on the sole hardly pigmented at all. The same layer in the skin of a white boy became pigmented after exposure to the sun. Hunter removed a melanotic tumour from below the jaw; such tumours were then included with those styled "fungus haematodes," as in the Museum specimen by Langstaff in 1812. Hunter was the first after Aristotle to advance knowledge concerning the Cephalopoda. The oldest of his specimens, still preserved, is the part of a huge calamary which Banks and Solander picked up off Cape Horn on Cook's first voyage. Hunter's observations included the discovery of the organ of hearing, and his collection supplied Owen with material for his classical descriptions.

William Lawrence, in 1818, in his lectures on physiology, zoology, and the natural history of man, described the varieties of the coloured races of mankind and aimed to put forward a rational view of the coloration of the negro. The negro was then held to rest under a primaeval curse, and the lecturer raised a storm of prejudice. Lawrence is now regarded as one of the founders of anthropology, and his lectures as a mine of carefully collected facts. Darwin completed the explanation. He said in his *Descent of Man*:

> "Hence it occurred to me that negroes and other dark races might have acquired their dark tints by the darker individuals escaping during a long series of generations from the deadly influence of the miasmas of their native countries."

Darwin gave to the Museum the painting of the piebald negro boy from South America; Everard Home that of the albino tiger; Jonathan Hutchinson a number of illustrations of leucoderma, vitiligo, and partial albinism. The important *Monograph on Albinism in Man* by Pearson, Nettleship, and Usher, reproduced these and other illustrations in the Museum, and the monograph includes references to much of the subject of this lecture up to 1911.[1]

Following Hunter, the occurrence of melanotic tumours began to be noted by veterinary surgeons; the earliest illustration in the Library, that by Noack in 1820, exhibits melanotic disease in the ano-genital region of a grey mare (Fig. 11). In the same year Fawdington published a coloured lithograph representing melanotic growths in man. In 1847 Haycock described internal tumours in a horse. The classical description of melanotic cancer was given by Paget in his lectures between 1847 and 1852; it was based on specimens still preserved in the Museum and in that of St. Bartholomew's Hospital. The Museum also contains important illustrations by Jonathan Hutchinson besides those already mentioned—for example, drawings of melanotic whitlow, of the unequal distribution of pigment in melanotic growths, and of the senile freckles which may become malignant.[2] Chimney-sweeps' cancer attracted the attention of English surgeons from Percival Pott to Butlin, who devoted three lectures to the subject in 1892. Since then there have come researches relating to the influence of gas-tar products, both as regards pigment formation and the production of cancer in mice. Mr. Sampson Handley, in a Hunterian lecture in 1907, described the spread of the melanotic pigment from the new growth to the surrounding tissues, and along lymphatics to lymphatic glands.

The Origin of Melanin Pigmented Cells from Epidermis.

The epidermal origin of the melanin pigment and of the pigmented cells admits of demonstration in several ways, as well as the transference of such cells from the epidermis into the dermis and deeper tissues. On the other hand, that cells definitely mesoblastic in origin can form pigment so long as no malignant change has set in is not demonstrable, the property of the non-cancerous mesoblastic cell being limited to the taking in of melanin pigment by the cells acting as phagocytes. When melanotic cancer has once started, then the mesoblastic cells take part in it, so much so that the structure of secondary growths resembles sarcoma.

The Formation of Melanin Pigment in the Cytoplasm of the Epithelial Cells lining the Ink-sac of a Cuttle-fish.

The formation of melanin pigment in the cytoplasm of epithelial cells occurs in the ink-sac of Sepia.[3] It is a process which was evolved in palaeozoic times; Belemnites, mesozoic relations of Sepia, had an ink-sac measuring up to a foot in length. The remains of the Cephalopoda and of the great lizards which fed upon them are found in strata between the coal measures and the chalk. The Museum specimens were found crushed flat in the Oxford clay at Christian Malford and were described by Owen. His description includes that of the ink-sac, the muscular

fibres, and a drawing of a Belemnite restored. In one specimen the eight uncinate arms are preserved (Fig. 1). The dried black pigment was proved to be identical with the ink of Sepia by Francis Chantrey. After triturating and dissolving it he made a sepia drawing which a distinguished painter pronounced to be tinted with Italian sepia of the best quality.

In Sepia the ink-sac is a diverticulum from the rectum, the fluid being discharged, however, towards the head. There is an orifice, duct, collecting sac or reservoir, and a loculated fundus formed by infolding of the sac walls where the ink is secreted. Mr. Burne has kindly given me stained sections which exhibit the epithelial lining, the cells, and pigment in all stages of formation as follows (Figs. 2 and 3).

(*a*) Columnar epithelium rests on a basement membrane; the cells have oval nuclei, with one or more nucleoli, many of which are dividing, surrounded by an alveolar arrangement of the cytoplasm. (*b*) The nuclei are in the deeper part of the cell; in the cytoplasm around the nuclei are dark dots which tend to lengthen out into rods, arranged perpendicular to the basement membrane. (*c*) The superficial ends of the rods have broken off into dark granules or have run together into black droplets, which occupy the superficial portion of the cell. Unpigmented cytoplasm having an alveolar arrangement surrounds the nucleus in the deeper part of the cell. (*d*) The superficial portion of the cell has become distended with pigment; it disintegrates on the surface like goblet cells of the intestine, and the liberated pigment mixed with mucus collects in the reservoir. The inky fluid is highly diffusible so that it affords the maximum amount of obscurity around the animal. An octopus being repeatedly irritated, at first ejects inky fluid, then fluid less black, until finally the fluid discharged is quite colourless. The fluid has also poisonous properties—a lobster turns on its back, helpless to resist.

Pigmented Cells Produced in the Epidermis Passing Down into the Dermis and Deeper Tissues.

In embryo frogs branched pigmented cells develop in the epidermis and pass downwards into subepithelial tissues.[4] The ova of frogs are at first unpigmented, then granules of melanin appear in the cytoplasm and serve to protect against the harmful effects of sunlight whilst the ova are floating in the water; for frog embryos at the time of the closure of the neural tube have been killed by exposing them to ultra-violet light rays.[5] Exposure short of a lethal dose causes the rayed epidermis to increase in thickness and multiplies the amount of pigment in the deepest layer of cells. At this stage the epidermis of the back of a tree-frog embryo exhibits numerous branched cells containing pigment, whilst under the epidermis there are no pigmented cells at all. At the next stage the branched pigmented cells push down processes through the basement membrane into the dermis (Fig. 4). The body of the cell with its nucleus follows, so that there is then a bridge between the epidermis and dermis (Fig. 5). Subsequently pigmented cells are to be seen lying in the dermis with a process stretching up into the epidermis. Finally all the pigmented cells may be found beneath the epidermis (Fig. 6).

The Formation of Melanin Pigment in the Eyeball.

Melanin pigment begins to appear in the epithelial cells forming the outer layer of the optic cup in the embryo chick at the forty-second hour of incubation, in the fourth month of the human foetus. Particles of pigment arise within the cells distinct from the nuclei; at first grey, the particles become black and rather rod-shaped. The pigmentation begins in the equatorial zone of the future eyeball and spreads forwards more rapidly than backwards. There is formed a single layer of hexagonal pigmented cells, lying external to the rods and cones, with numerous processes into which pigment particles pass as the processes stretch down between the rods and cones. About the eleventh day in the incubated chick, in the seventh month of the human foetus, pigmented cells are found alongside the blood vessels of the choroid which has developed from mesoblast. The anterior margin of the retinal pigmented epithelium grows forwards beyond the ora serrata to furnish the pigmented cells of the uveal layer of the ciliary bodies and iris. The full pigmentation of the posterior layer of the iris is not complete at birth.

Scattered Foci of Melanin-pigmented Cells in Deep Tissues.

The pigmented cells of the epidermis and of the eyeball serve a useful purpose; no useful purpose has been assigned to collections of pigmented cells scattered among internal structures.

It may be explained that scattered foci of pigmented cells have reached their position during embryonic development.[6] Embryos of fish such as larval eels are at first transparent and pigment can be seen to develop in the eye and epidermis whilst the blood is still colourless. Embryos of bony fish in which the cartilage has been stained to contrast with the melanin pigment serve to demonstrate that pigment cells spread out from around the neural groove and canal in accordance with the segmentation into the metameres (Fig. 7). There is a primitive arrangement of pigmented cells on the surface along dorsal, ventral, and lateral lines and into the radiations of the fins. Sections through such embryonic fish exhibit deeper collections of pigmented cells, also corresponding to the metameric divisions. Stripes, patches, and markings on the coats of higher animals suggest a connexion with the primitive vertebral segments of the embryo.

It seems, therefore, a rational explanation that melanin pigmented cells, whether superficial or deep, have primarily developed around the neural tube, originally for the protection of the central nervous system. The pigmented cells have spread first into the epiderm, then deeper into the mesoblast of the immediate neighbourhood, and further have been carried away in the parietal and visceral layers of mesoblast along with outgrowing nerves, especially sympathetic nerves. Upon this the following classification is based.

A. *Skin*:—(1) *Epidermis:* Melanin pigment in the cells of the rete Malpighii, to a less extent in those of the rete spinosum, in the corresponding epithelial cells which produce shafts of the hair, also in the dendritic cells of Langerhans lying between the foregoing. The pigmentation of the epidermis varies from a deep black on exposed surfaces of the negro, to be hardly perceptible on most of the skin of blond races when not exposed to sunlight. Yet white races always show considerable pigmentation in the ano-genital skin and the areolae of the nipples.

(2) *Dermis:* Pigmented cells with branched processes occur singly, in scattered groups, in patches and sheets. Some lie close under the epidermis, some adjacent to the subcutaneous tissue. They originate as dendritic cells which have penetrated from the epidermis downwards into the dermis, whether already pigmented melanophores, or as colourless melanoblasts which become pigmented in the dermis. The mesoblastic cells of the dermis, as distinguished from cells of epidermal origin, have phagocytic properties and take up pigment freed by the breaking down of epidermal cells. The pigment may be so finely divided as to appear merely a dusky stain, or in the form of granules which pass from the epidermis along lymphatic channels. In lower animals the pigmented cells of the dermis serve a useful purpose in addition to the protection against excess of sunlight—colour is changed voluntarily and reflexly, in mimicry of surroundings; colour serves to differentiate species, and to distinguish sex during the breeding season. The subepidermal pigment cells are closely connected with radiating muscular fibres and nerve fibres, and under the control of the central nervous system, through sympathetic nerve fibres, cause changes in colour: on the one hand pigment granules collect in the body of the cell; on the other hand the pigment spreads out into the cell processes, the action being similar to that of the cells of the retinal epithelium covering the rods and cones. The differences in colour are partly due to the circulation of blood and to the varying translucency of the overlying skin; hence the change of colour in the dying and dead fish. Whatever the useful purposes served by pigmented cells in the dermis of animals, in human beings the scattered remnants are of no use. Groups of pigmented cells are found deep in the skin, especially of the back in the sacral region. This is the case to a small extent in blend races, but is much more marked among Mongolian, Eastern Asiatic, and Mediterranean races. Infants for some time after birth exhibit bluish, violet, or mulberry-coloured patches, scattered over the sacrum, buttocks, or even the shoulders. There may even be stripes reminiscent of vertebral segmentation. The patches are bluish rather than black, although the pigment in the cells is melanin. This is an optical effect of the semi-translucent overlying skin, as when tattooing is done with indian ink. As the skin thickens after birth the patches gradually become invisible, generally before 2 years of age.[7 8]

B. *The Eyeball.*—When fragments taken from the retinal pigment epithelium of an embryo chick are added to a cultivation *in vitro* of small pieces of living tissue, cells are seen to ingest granules of pigment.[9] This tends to show that the pigmented cells found outside the limits of the structures formed by the retinal pigment epithelium—namely, in the choroid and ciliary processes—may be derived from one of two sources: epithelial cells may have grown outwards from the original retinal pigment layer, or mesoblastic cells, fibroblasts, acting as phagocytes, may have ingested the pigment. In darker races scattered groups of pigmented cells are met with in the ciliary muscle, in the sclerotic, in the ocular conjunctiva, with much individual variation. In sheep in particular pigmented cells are carried along with ingrowing nerve fibrils into the limbus of the cornea.

C. *Collections of Pigmented Cells around the Central Nervous System.*—Patches of pigment occur scattered in the pia mater about the base of the brain and on the cervical and lumbar spinal cord. The condition is more noticeable in some animals, such as sheep; the brain of the crocodile in the Museum is enclosed by a dark sheet of pia mater. Symmers[10] noted in the course of *post-mortem* examinations of modern Egyptians a particularly well marked pigmentation of the pia mater. Melanin pigment is regularly present in the olfactory epithelium and in that of the labyrinth.

D. *Perineural, Perivascular, and Pericoelomic Groups of Pigmented Cells.*—These are found in the course of nerves, in nerve ganglia, in the wall of the heart and large blood vessels, in retroperitoneal and mesenteric connective tissue. In calves slaughtered for veal scattered pigmentation in the lungs, liver, along the trachea and oesophagus, in retroperitoneal tissue, along the sheaths of the sciatic and crural nerves, has attracted attention in the course of meat inspection. In full-grown cattle this becomes much less marked,[11] whether obscured by the thickening of tissues or because removed by absorption. In sheep melanin pigmentation is marked in periarterial and perineural tissues, in the endocardium and inner coat of the large arteries.[12] In the developing chick pigment is carried from the feathered areas inwards as far as the periosteum.

Chemical Formation of Melanin.

Note on the Chemical Relationships of Melanin.

The following formulae indicate possible steps by which melanin is formed.

(Revised by H. Wilson Hake, Ph.D.)

Methylamine	$NH_2—CH_3$
Ethylmethylamine	$CH_3—CH_2—NH—CH_3$
Ethylomethylamine	$CH_2OH—CH_2—NH—CH_3$
Propionic acid	$CH_3—CH_2—COOH$
Hydroxypropionic or ethylidenelactic acid	$CH_3—CH.OH—COOH$
Aminopropionic acid or alanine ...	$CH_3—CH.NH_2—COOH$
Hydroxyaminopropionic acid or serine	$CH_2OH—CH.NH_2—COOH$
Thioaminopropionic acid or cystein...	$CH_2SH—CH.NH_2—COOH$
Disulphide of cystein or cystin ...	$CH_2—S—CH\,NH_2—COOH$ $\vert$ $CH_2—S—CH\,NH_2—COOH$
Phenol	C_6H_5OH
Catechol or pyrocatechin, and hydroquinone	$C_6H_4(OH)_2$
Tyrosin or hydroxyphenylalanine ...	$OH.C_6H_4—CH_2—CH\,NH_2—COOH$
"Dopa" or dihydroxyphenylalanine	$(OH)_2C_6H_3—CH_2—CH.NH_2\,COOH$
Adrenaline or dihydroxyphenylethylomethylamine	$(OH)_2C_6H_3—CH.OH—CH_2—NH.CH_3$
Pyrrole	C_4H_4NH NH HC CH ‖ ‖ HC— CH
Indole or benzopyrrole	
Skatole or methylated indole	
Tryptophane or indole alanine	
Tyrian purple—dibromindigo	

The Formation of Melanin from a Colourless Mother Substance—Melanogen.

Melanin is obtained: (1) by macerating the skin of a negro—the total amount in the whole of the skin has been estimated not to exceed 1 gram; (2) from the ink of a cuttle-fish; (3) from a melanotic tumour. From whichever source there seems to be no essential difference in the melanin. In the course of analysis of melanotic fluid two portions may be distinguished—a sulphur-containing portion, and a portion blackened by oxidation. The amount of sulphur has been estimated to vary from 5 to 12 per cent., whereas in the original protein molecule the amount of sulphur does not exceed 2 per cent. In the living epidermis most of the sulphur is found in the keratin of the corneous layers, in the hair and feathers. In the breaking up of protein molecules the sulphur mostly passes into cystein and cystin. Freed from all traces of blood, melanin does not give the reaction for iron and the blood pigment has no part in its formation.

The idea of a colourless mother substance, melanogen, which becomes by oxidation melanin, originated with the discovery of Thormählen that the urine of patients suffering from secondary melanotic cancer of the liver turned dark on oxidation. The process occurs under simple exposure to the air, but is intensified by treating the urine with oxidizing agents.[56] Further researches have shown that melanogen is present in the basal layer of the cells of the epidermis, also in the epithelial cells of the hair follicles by which hair is formed, including the dendritic cells lying between.

Fresh pieces of dead skin, also sections of fresh skin cut by a freezing microtome, darken when kept for some days in an incubator. The darkening is much more rapid when the pieces or sections are exposed to ultra-violet light rays. Pieces of skin or sections made as above from brunettes or patients dead of Addison's disease are still further darkened. The same happens in dog's skin already darkened by removal of the adrenals. On microscopic examination this darkening is seen to be the result of the formation of granules of melanin pigment in the epithelial cells. Darkening by the formation of melanin from melanogen is also produced by chemical reagents. Solutions of tyrosin and of adrenaline act weakly; a much more active reagent was discovered by Bruno Bloch, professor of dermatology in Zürich;[13] it is nearly allied in composition to tyrosin. He named it for short "dopa," and obtained it from embryos of the broad bean. Fresh skin and sections cut with a freezing microtome treated with a 1 pro mille solution of "dopa" take on a smoky grey stain which deepens by the formation of brown and black granules (Fig. 8). The process is one of oxidation which is prevented by an atmosphere of nitrogen; it is favoured by warmth in an incubator, but inhibited by overheating. The darkening is restricted to the epithelial cells in the basal layer of the epidermis and to the cells forming the hair. The dendritic cells are best demonstrated in horizontal and oblique sections, when both the cells and their processes are seen to be deeply stained by the "dopa" solution (Fig. 9). The density of staining varies from cell to cell, and there are individual variations in accordance with the natural colour of the skin. The "dopa" reaction further serves to show that melanogen is absent from patches of leucoderma or vitiligo and from the skin of albinos; skin from such sources when treated with "dopa" solution fails to stain; neither the cells of the rete Malpighii nor of the hair follicles become darkened.

In the human foetus the "dopa" reaction is yielded by the cells of the epidermis and hair follicles before any appearance of pigment. The embryonic cells of the retinal epithelium before the commencement of the formation of pigment—that is, before the fourth month in the human foetus—are likewise stained by the "dopa" solution. On the other hand, pigmented cells in the choroid as well as those in the dermis are not further darkened by the "dopa" solution which tends to indicate in them the absence of melanogen, and that these connective tissue cells of mesoblastic origin are not melanoblasts, but merely melanophores. When melanin is injected subcutaneously such connective tissue cells take up melanin by a process of phagocytosis.

The cells in a pigmented naevus are deeply stained by the "dopa" solution, but so long as no malignant change has set in connective tissue cells are not affected (Fig. 10). When, however, melanotic cancer has supervened then there is a staining by "dopa," not only of epithelial but also of connective tissue, including endothelial cells. This may be taken to indicate that with the setting in of the malignant process there is a production of melanogen to excess.

Bloch holds that the conversion of melanogen into melanin is due to the interaction within the cells of an enzyme—namely, an oxidase, such as causes vegetable and animal materials to change colour. The activity of a melanin oxidase is in accordance with the fact that the

"dopa" reaction does not occur in an atmosphere of nitrogen and is destroyed by heat. The milky juice of plants which yield lacquer is turned black by laccase; tryosin is made to change colour up to black by an enzyme, tyrosinase, found in many vegetable and animal materials. A familiar reaction is produced by an enzyme contained in red corpuscles on guaiacum in the presence of oxygen. The blood of some insects turns black on exposure to air from the formation of melanin.[14]

Another set of experiments has the same bearing. Quattini[15] injected pyrrole, also indole (benzopyrrole) and skatole or methylated indole, under the skin of rabbits, with the result that nine to eighteen days after the injection the skin of the animals became darkened by brownish lines and networks, spots and patches, along with an increased growth of pigmented hair. The pigment was very like melanin; it was not produced by the injection into an albino rabbit, nor in the white areas of animals having the skin partly white, partly coloured. In the albino rabbit the growth of hair was stimulated, but the hair remained unpigmented.

Tar painted repeatedly upon the skin of grey or brown mice for several weeks caused a pigmentation of the skin by the formation of melanin in the epidermis. This happens sometimes before the changes set in which lead up to cancer. In white mice, however, whilst precancerous and cancerous changes are produced a preliminary pigmentation of skin does not occur from the rubbing in of the tar. This appears to confirm the absence of melanogen in white mice.[16 17 37]

To demonstrate the presence of melanogen in melanotic cancer D'Agata injected pyrrole into non-pigmented tumours, rapidly developing secondary to a melanin-pigmented primary tumour in a dog. Pigment was afterwards found but was absent following control injections of salt solutions.[64]

Human melanotic cancer has not been transplanted into mice.

Clinical Observations on the Pathological Formation of Melanin.

The body louse, *Pediculus vestimenti*, when it punctures the skin with its haustellum to suck up blood, at the same time injects fluid from its salivary glands which produces a black spot of melanin pigment in the deepest layer of the epidermis. An emulsion of the insect's salivary glands has the same effect when injected; fluid from its stomach fails to do so. A man who presented the characteristics of phthiriasis had his back covered by black spots except over a white patch the size of the palm of the hand. This white patch, whether the result of congenital albinism or acquired vitiligo, had remained entirely unpigmented, owing presumably to the absence of melanogen.[18 19]

Women working in ill ventilated coal-tar factories, after inhaling fumes for a time, have exhibited a gradually increasing pigmentation of previously unpigmented skin.[20 21]

Arsenic taken by susceptible people to excess produces a pigmentation of the skin along with a keratosis affecting especially the palms of the hands and soles of the feet.[22 23]

In the earlier part of last century, when silver nitrate was administered freely by the mouth, or applied over long periods to the conjunctiva, argyria, an intra vitam staining by silver nitrate, occurred in some individuals. The face and other parts took on a patchy and diffused pigmentation of a slaty hue; the conjunctiva became bluish. When fresh skin, or sections of skin cut with a freezing microtome, are treated with a 1 pro mille solution of silver nitrate the silver nitrate combines with melanin pigment to darken it; afterwards there is a reduction to silver oxide. Catechol or pyrocatechin and its derivatives react with silver nitrate in the same way, and this is therefore another bit of evidence as to the composition of melanin.

Variations as to the presence or absence of melanogen in the skin may be held to account for individual differences in the pigmentation of the skin which follow the application of cantharides, the exposure of the skin to sunlight and artificial light rays—patches of leucoderma and vitiligo proving insusceptible. The effects of ultra-violet light rays also vary with the actual melanin already present—a brunette escapes sunburn, a blond suffers temporary irritation, or freckles are produced, temporary or persistent.

Increased pigmentation, general in causation, set up by changes in metabolism, appears to be connected especially with disturbances of endocrine functions.[24] Instances of this occur in connexion with the adrenals, exophthalmic goitre, liver diseases, and the female genital organs. The brown, waste, wear and tear pigment, found in the heart, liver, and under the mucous membrane of the colon consists of melanin, and the term "haemosiderin" is a misnomer.[25 26] Further, there is the increased pigmentation which supervenes in the course of various cachexias. A boy suffering from complications following scarlet fever had browning of the skin. Bits of his skin excised at intervals yielded the "dopa" reaction until the boy's general health began to improve. As the brown staining cleared off the "dopa" reaction weakened.

The peculiar form of increased pigmentation in young people undergoing sunlight and open-air treatment for tuberculosis appears to result from an improvement in metabolism. It is accompanied by increase of weight, muscular development, and a greater production of body heat so that clothing can be dispensed with. Gauvain[27] states that a failure to develop the pigmentation of the skin indicates a lack of resistance and a failure to overcome the disease. This, however, may be temporary, the increase in metabolism being checked until some latent source of sepsis is discovered and eradicated.

Adrenaline and Melanin Derived from a Common Mother Substance.

The note on chemical formulae and various preceding statements lead up to the explanation that the pigmentation which occurs in Addison's disease, also that in dogs after the removal of the adrenals, is due to the accumulation of a mother substance common to adrenaline and melanin. When the adrenals cease to take up this mother substance and convert it into adrenaline, the excess collects in the cells of the epidermis as melanogen to form melanin by oxidation. Pigmentation of a patch of vitiligo was obtained by injecting adrenaline, after which the patch was exposed to ultra-violet light rays.[28]

A solution of melanin was found to have the same effect on the blood vessels of a frog as one of adrenaline, only weaker; on the heart of a rabbit the solution of melanin exceeded in effect that of adrenaline.

Here I just mention the resemblances between the melanin produced in the ink-sac of Sepia and the Tyrian purple of the ancients, which some fishermen still use for marking their linen. Molluscs, Murex, and Purpura—*Murex brandaris* in particular—have a gland connected with the rectum composed of elongated columnar epithelium which secretes a fluid, originally colourless. The fluid under sunlight turns yellow, blue, reddish, violet, and purple. From the glands P. Friedländer[29] obtained dibromindigo in the form of crystals having a coppery hue. Roaf[30] found that fluid from the glands acted like adrenaline in raising blood pressure. In the course of preparation of the purple there was given off a sulphurous garlic-like odour, also a faecal odour such as is produced by substances allied to indigo; Pliny in describing the preparation of the dye spoke of this "virus grave in fuco."

Observations on the Loss of Pigment from the Hair.

Metchnikoff in his studies on Old Age assumed that pigment was actually withdrawn from the shafts of the hair, but subsequent observations have demonstrated that coloured, grey, and white hair are produced as such, according as the epithelial cells producing the hair also form melanin or not. Tales of the sudden blanching of hair may be treated with scepticism.

Observations regarding the growth of the summer and winter coat of the variable hare, stoat, etc., show that the change in autumn is due to a growth of non-pigmented hair whilst the brown hair of the summer coat falls out; early in the autumn, on separating the long brown hairs, short young unpigmented hairs are seen to be protruding from the skin. In the spring the variable hare gets rid of its winter coat, not only by licking, but by also "mouthing".

W. G. SPENCER: MELANOSIS (MELANIN: MELANOMA: MELANOTIC CANCER).

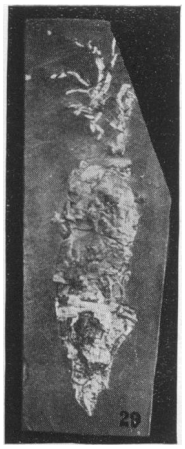

FIG. 1.—Belemnite with ink-sac and eight uncinate arms, in Oxford clay. (Museum specimen.)

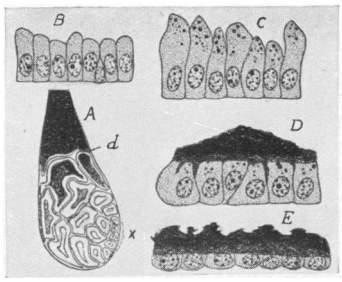

FIG. 3.—Diagrams from Dalgren and Kepner. A, Ink-sac; ×, loculated fundus; *d*, reservoir; B, C, D, E, stages of melanin formation.

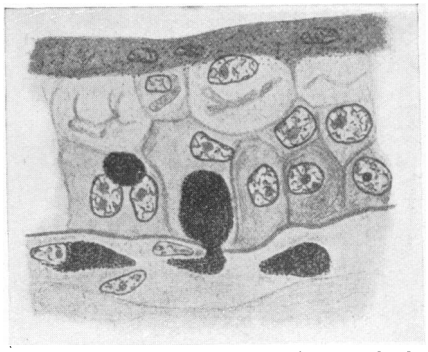

FIG. 4.—Tree-frog embryo: section from back. Melanophore in epidermis with process stretching down into dermis. (Kornfeld.[4])

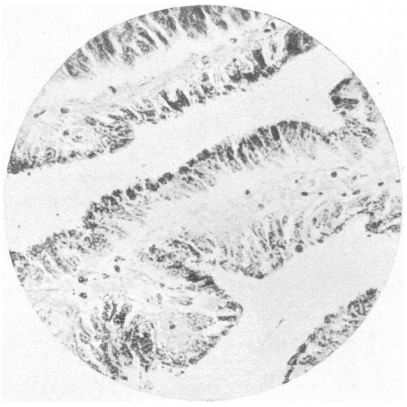

FIG. 2.—Loculated ink-sac of sepia in section: epithelial cells exhibiting stages of melanin formation. (Mr. Burne.)

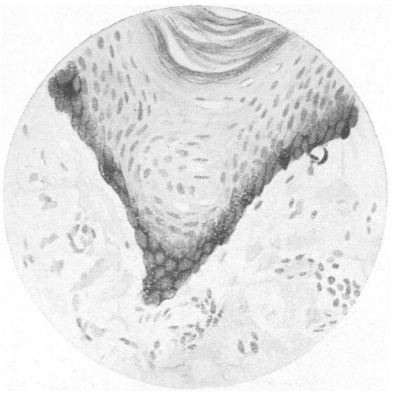

FIG. 8.—Normal blond skin—vertical section. Melanogen in basal cells of epidermis stained with "dopa": melanophores in dermis not stained; nuclei counterstained green. (Bloch.[18])

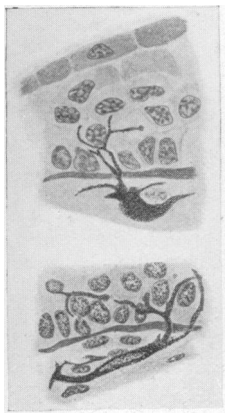

FIG. 5.—Tree-frog embryo—later. Melanophores in dermis with processes extending up into epidermis. (Kornfeld.[4])

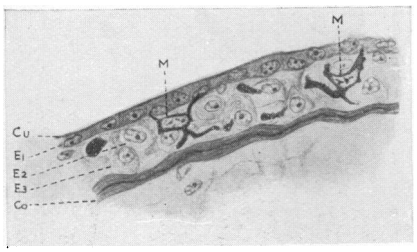

FIG. 6.—Tree-frog embryo: skin, subcutaneous tissue, muscle. All melanophores in subcutaneous tissue. (Kornfeld.[4])

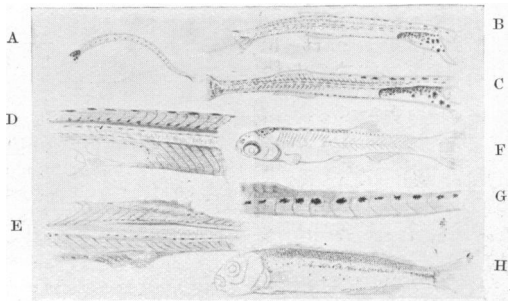

FIG. 7.—Embryonic bony fish—cartilage stained; segmental arrangement of melanophores. A, Atherina: melanophores lateral lines. B, Atherina: melanophores dorsal, lateral, and ventral lines; radiations fins and branchiae. C, Atherina—older. D, Atherina; longitudinal section showing spinal cord, notochord, somites, and intersegmental lines. E, Atherina; fin radiations and intersegmental lines. F, *Alburnus lucidus:* metameric arrangement of melanophores. G, *Alburnus lucidus:* melanophore in each segment. H, Box boops—2 cm. in length; golden stripes when full-grown. (Bolk.[6])

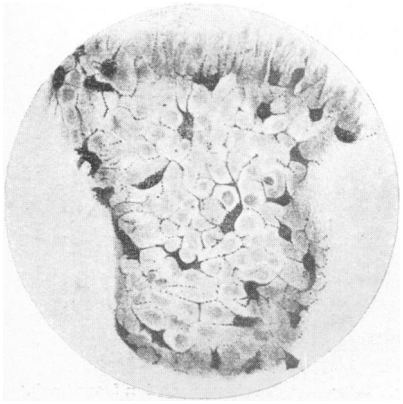

FIG. 9.—Normal blond skin—horizontal section. Dendritic cells of Langerhans deeply stained by "dopa." (Bloch.[13])

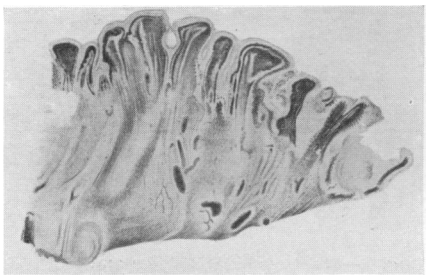

FIG. 10.—Normal blond skin. Rugose mole stained by "dopa." (Bloch.[13])

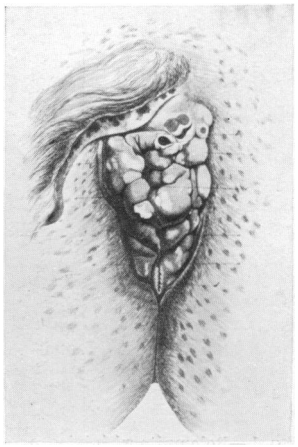

FIG. 11.—Ano-genital region of grey mare with melanotic disease. (Noack, in Library.)

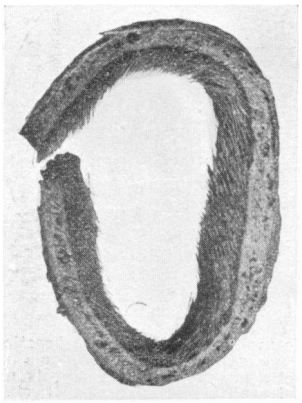

FIG. 12.—Hair'ess skin under tail of white horse. Collections of melanophores around deep coiled ends of sweat glands. (Jaeger.[11])

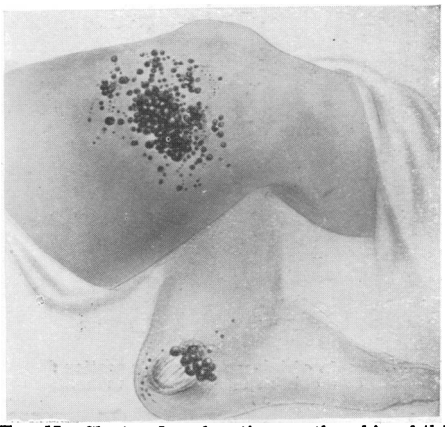

FIG. 15.—Clustered melanotic growth: skin of thigh and melanotic whitlow. (J. Hutchinson, drawing in Museum.)

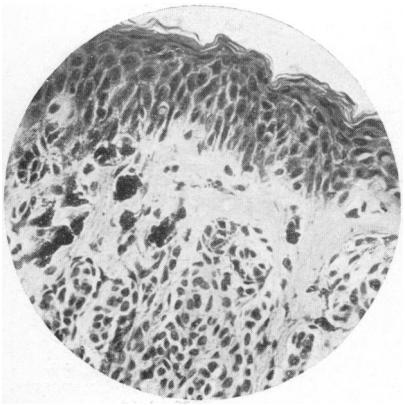

FIG. 13.—Vertical section through surface of mole which had become malignant. Pigmented cells penetrating downwards from epithelium. (W. G. S.)

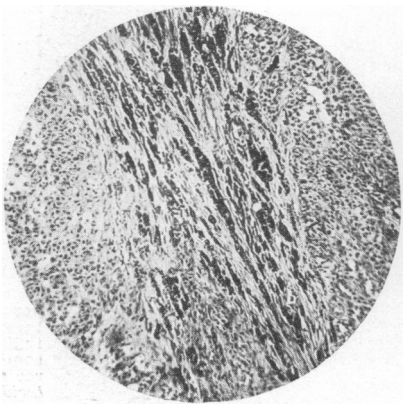

FIG. 14.—Deeper portion of same. Pigmented cells which have become oval and spindle shaped, cut some longitudinally, some transversely. (W. G. S.)

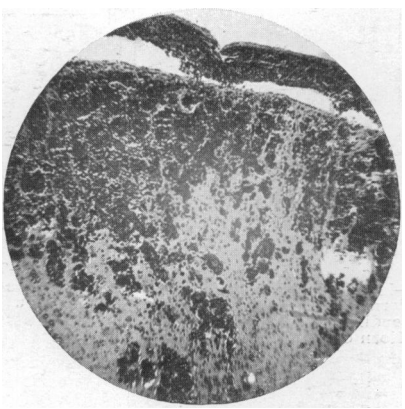

FIG. 16.—Melanotic cancer spreading from pia mater into brain. (W. G. S.)

hair, some of which hairs are found in its faeces. Under the long unpigmented hair of the winter coat, short pigmented hairs are to be found.[1]

Loss of the Pigmented Hair in Grey Horses followed by Melanosis.

Grey horses after the age of ten years tend to become white owing to the loss of pigmented hair, including the hair of the mane and tail. With increasing age these animals develop some form of melanotic cancer with such increasing frequency as to give rise to the statement that if a white horse lives long enough some degree of melanotic new growth will be found on a complete examination after death.[31] Horses which keep their hair dark very rarely suffer. The skin covered by the white hair is likewise unpigmented, but the pitch-black pigmented skin, free from hair, of the ano-genital region, mammae, scrotum, and folds of the prepuce, also the margin of the lower lip, remains unaltered. This deeply pigmented hairless skin is a site of predilection for the starting of melanotic disease (Fig. 11). It is first noticeable as small black nodules which run together into tumours and then come to be embedded in a general thickening which later has the characteristic appearance of rugose elephantiasis. Preceding this naked-eye appearance there have been found microscopic changes; when vertical sections are made through the skin under the tail of an aged white horse isolated pigmented spots may be seen, in particular near the deep coiled ends of the sweat glands (Fig. 12). On the other hand, examination of the same skin taken from an old horse which has retained pigmented hair fails to discover such collection of pigmented cells. The melanotic disease does not extend superficially beyond the black hairless areas, but removal is only practicable in the case of melanotic elephantiasis of the folds of the prepuce. The inguinal glands enlarge early, but remain circumscribed and do not infiltrate. The two commonest external manifestations of secondary disease are in the parotid region, and between the scapula and spine, deep in the rhomboid muscles. Similar instances occur in human beings; a case of scapular metastasis was described by Cairns.[32] From the ano-genital and inguinal regions the disease spreads to pelvic and lumbar glands, to the abdominal and thoracic viscera. Black cords and chains of nodules are found in the retroperitoneal tissue, masses in the spleen, etc., at the root of the lungs, and around the base of the heart. There is a marked absence of general wasting, the animal working until it dies suddenly. The enormous growths cause mechanical obstruction by displacement of tissues without general infiltration. Whilst in human beings the growths commonly remain solid, in horses they are often cystic. Haycock wrote his note with the black fluid contained in one of the cysts, just as Cuvier drew a sepia with the animal's ink. A cystic tumour of the spleen or lung may rupture and cause immediate death of the horse.

Congenital Melanomas becoming Melanotic Cancer.

Pigmented naevi exhibit melanin granules in the basal layer of the epidermis, and to a variable but much smaller extent in the rete spinosum. Moles which are rugose on the surface have fewer rows of cells in the rete spinosum, and an increased thickness of the corneous layers.

The original structure of the pigmented naevus consists of a regular arrangement of cells, the epidermis being clearly distinguished from the dermis. During adult life there is a slow degeneration, variable in degree, to be recognized by a full examination of a number of specimens.[33] The epidermis and dermis become less sharply defined; there are branched pigmented cells in the dermis, some are epithelial cells which have dipped down, some connective tissue cells which have taken up pigment freed by the breaking down of epithelial cells (Fig. 13). Free granules of pigment are found in lymphatic spaces and cells may have a dusky stain. These changes are to be noted before any sign of cancer, but also in the areas surrounding the commencement of cancer.[34]

The malignant growth begins in the lowest layer of the epidermis, and resembles either one of the varieties of rodent ulcer or squamous-celled carcinoma. Just as sections of chimney-sweeps' cancer show granules of soot in the cells growing downwards,[35] so also in melanotic cancer the growing margin of cells exhibits melanin granules. As the epithelial cells grow down into the dermis they tend to assume an oval or spindle shape (Fig. 14), later on an alveolar arrangement; they break into lymphatics, invade the wall of blood vessels, and set up haemorrhage.

The masses of melanotic cancer in lymphatic glands and internal organs are composed of oval and spindle cells. Whilst recent observations indicate epidermal cells as those which commence the malignant change, the appearances of the tumours have led them to be termed sarcomata. Paget, in his lectures, generally used the term "melanotic cancer," and I have followed him in that respect. Discussion has proceeded much on the same lines as earlier debates concerning the origin of the elements composing a scirrhous cancer of the breast, also as regards the cancers produced by rubbing tar into the ears of animals.[36] [37]

Melanomas are very common among darker races, indeed more so than among white races, yet this does not render them prone to melanotic disease. No great stress can, perhaps, be laid on this point, because such races are generally reported to be less susceptible to cancer in general. Seligman[1] noted among natives of New Guinea that pigmented moles were common on all parts of the body, both in men and women. Yet no case was seen or heard of in which a pigmented mole had tended to spread or give rise to tumour formation. Among 8,000 hospital surgical in-patients belonging to dark races in Constantinople[38] there were 390 cases of carcinoma, 125 of sarcoma, and 3 of melanotic cancer; two of the latter had grown from the relatively unpigmented sole of the foot, and one involved the gall bladder after the patient had suffered from what had been called piles. Among 12,000 surgical out-patients there were no cases; among 2,000 eye cases there were two—one originating in the conjunctiva, the other in the ciliary body. The occurrence seems likewise rare among negroes in the United States; the only case I have noted, one described by Gilchrist,[39] began on the relatively unpigmented sole of a negro, as in the two Constantinople cases.

An exceptional case was seen by me in conjunction with Dr. Redmond Roche. A boy aged 5 was the son of brunette parents both of whom presented numerous superficial pigmented moles; on the dorsum of one of the boy's toes was a superficial ulcer with a black surface which had been treated as a chilblain. On two other toes were quiescent pigmented moles. In the corresponding groin was a gland enlarged to the size of a hazel nut. Examined after excision the ulcerated mole exhibited pigmented cells and haemorrhages in the base of the ulcer; the corresponding enlarged gland showed foci of pigmented cells and haemorrhages. The other two proved to be quiescent epithelial melanomas. I cannot give a subsequent report on the case, but at such an age malignant disease may be considered out of the question.

Pigmented spots acquired after puberty or late in life may also become malignant. Hutchinson described several varieties. By 1886 he had seen half a dozen cases of melanotic whitlow; many more instances have been described since that date, all remarkably alike, and all pursuing a malignant course (Fig. 15). They are instances of melanotic squamous-celled carcinoma. The specimen described by Bowlby[40] occurred on the great toe—half is in the College Museum, half in that of St. Bartholomew's Hospital. In Csaki's case the toe-nail from childhood had separated on many occasions before melanosis set in.[41]

Hutchinson also described the senile freckles, lentigo senilis, which occasionally become malignant.[2] [42] The clinical course and structure of the growth is then as a rule that of rodent ulcer followed ultimately by a metastasis.

A slight puncture of the skin may leave a pigmented spot which subsequently becomes the seat of melanotic cancer. In Eve's case a woman at the age of 27 ran a splinter into the hypothenar eminence, and a black spot persisted there for twelve years, until after being again accidentally pricked. Melanotic cancer then started, of which she died eleven months later.[43] Two of the Museum specimens are from a man aged 55 in whom melanotic cancer supervened from a puncture by a horn under the jaw three months before. The man died of the disease fifteen months after the injury.

Metastasis of Melanotic Cancer.

Once the malignant change has started metastasis follows, whether it becomes apparent soon or late; there are extra-

ordinary instances of delay in its appearance. Coley reported 91 cases treated by excision, also by his toxins, radium, and *x* rays. The primary treatment of a pigmented mole which had begun to spread failed, whichever of the above means was used.[44] In Küttner's Klinik from 1890 onwards there were 39 cases of melanotic cancer. Of 26 submitted to operation 4 survived the first operation for five years, soon after which 3 died of generalized melanotic cancer.

A few individuals appear to present an extraordinary resistance to the extension of the cancer.[45]

Chauvin operated four times upon a woman in the course of twenty-two years.[46] At the age of 28 a brown mole which had ulcerated was removed from the right naso-labial furrow; it exhibited under the microscope the structure of melanotic cancer. Four years later a similar nodule was removed from the right malar region, and two years subsequently a further recurrence at the same spot. For the fourth time, the patient being then 48, two nodules of melanotic cancer, placed on the line of the lymphatics in the course of the facial artery, were cut out. There was then no sign of lymphatic gland enlargement or of metastasis.

Eve[43] described the case of a woman who twenty years before had a melanoma cut out from the dorsum of the hand. There was a recurrence *in situ* ten years later, and a second recurrence at the end of twenty years, when there were in addition metastatic growths in the axilla and on the temple.

Mr. Jonathan Hutchinson, junr., verbally informed me that he saw a woman who for ten years had discharged a melanotic fluid from the stump after the removal of the eyeball by Tay for melanotic cancer.

A widely diffused pigmentation of the skin has occurred in the course of generalized melanotic cancer. Cases have been described by Fergusson, Legg, Matsunga,[47] and Tietze. Such increased production of melanogen and melanin has been previously emphasized.

Melanotic Cancer of the Eyeball.

Both in men and animals there occur abnormalities of pigmentation in all grades down to complete albinism. The parti-coloured iris is a slight abnormality; the so-called "wall eye" is common in the horse, and includes a greater abnormality affecting the uveal layer in the choroid and ciliary bodies. But in the most complete albinism the retinal pigment epithelium is constantly normal.[1]

Mr. Foster Moore, in the course of routine examinations of the ocular fundus, has noted patches of pigment, which, however, had given rise to no defects of vision. The patches are situated near the optic disc not more than two diameters of the disc away, having an area of a quarter to four times that of the disc. They have a homogeneous colour, likened to that of blue ointment, an oval or circular contour, and a feathered edge with the retinal vessels, normal in character, crossing in front. One patch examined *post mortem* showed a structure corresponding with a mole on the skin, and so these patches appear to be congenital in origin. The patches remained quiescent under observation, and no relationship with melanotic cancer has been established.[48]

In spite of the frequency of "wall eye" in horses, a melanotic cancer of the eyeball is rare even in the grey horse which turns white.

Melanotic cancer arises in the eyeball as a rule after middle life. Whilst it generally arises from the pigmented layers within the eyeball, it may start external to the eyeball in the conjunctiva or eyelid, when it may be in a congenital or acquired spot of pigment.[52] It has often followed upon an injury, but the onset may be delayed.

In Lawson's case the eyeball had been injured and shrunken for twelve years.[49] In Keown's case the patient had been for long exposed to an excess of electric light.[50] In Pfingst's case the disease occurred in two brothers;[51] in Silcock's in a mother and daughter. In Robinson's case a pigmented spot appeared on the outer surface of the upper eyelid and gradually spread over the forehead and cheek; later there was extension to the mucous membrane within the cheek and to the opposite eyelid.[53]

Melanotic cancer as a rule has advanced so far before the eyeball was removed that patients have died of metastasis even although there has been no recurrence *in situ*. The usual course is for a secondary mass in the liver, etc., to be attended by melanuria and to cause the patient's death within three years.[54] Death may, however, be delayed; there may even be extraordinary delay—namely, for 10, 12, 16, 17, and even 24 years in Olbert's case.[55] Except after melanotic growths of the eyeball, melanotic cancer of the liver with melanuria is rather the exception, otherwise one might almost believe such prolonged intervals to indicate an origin *de novo*.[56]

Melanoma and Melanotic Cancer of the Hard Palate.

Congenital patches may be noted on the hard palate, also on the inner aspects of the cheek and tongue in dark races—for example, Dravidian races in India. They have also been stated to appear for the first time in middle life and afterwards to spread. When cut out early the structure is found to be that of quiescent melanomas. More than twenty-five cases have been recorded of melanotic cancer of the hard palate. Treatment by excision, *x* rays, radium, diathermy have all alike failed to arrest the spread of the disease.[57]

Melanotic Cancer of the Abdomen.

Melanotic cancer in the abdominal cavity is usually secondary. As to a primary origin in the abdomen recorded cases have not been completely investigated—for example, as to the possibility of a supposed benign mole in the skin having undergone a malignant change discoverable only by microscopic examination. With this reservation melanotic cancer has been described as arising in the suprarenal capsule on one or both sides, in the ovary, urinary bladder, and gall bladder. The general explanation would be that the origin has been in one of the congenital patches of pigment which have been classified as perineural, perivascular, pericoelomic.

Melanoma and Melanotic Cancer in the Ano-genital Region.

This is an area which exhibits some pigmentation even in blond races. Pigmented moles are common on the external genitals of dark women, and in Indian women pigmented patches have been noted on the wall of the vagina and cervix uteri. Eardley Holland collected fifty-two cases of melanotic cancer of the vulva, of which number only one woman was free from signs of recurrence after three years.[58] A melanotic cancer of the vulva may be secondary; in Doran's case it followed upon an adrenal tumour, and he included references to two similar cases. A melanotic cancer of the penis is of rare occurrence: Shattock showed how readily the unpigmented glans of the negro becomes pigmented when uncovered. Primary melanotic cancer of the anus has been in its earlier stages confused with piles. In the negro the pigmentation of the skin is sometimes continued irregularly within the anus, and such an explanation may be given of the starting of a melanotic cancer in the rectum.[59] In Heaton's Museum specimen a man aged 48 had had haemorrhoids for twenty-five years when melanotic cancer set in, and after his death seven months later there were found invasion of lympathic glands and a nodule of melanotic cancer on the surface of the liver.

Perineural Melanotic Cancer in the Pia Mater of the Brain and Spinal Cord.

In a few cases it has been possible to define the situation in which the growth started. In Hirschberg's case it commenced at the level of the eleventh dorsal vertebra;[63] in Ogle's case in the pineal body, when the pigment may be related to the so-called median eye of the lizard Hatteria or Sphenodon.[60] MacLachlan described an extensive pigmentation associated in children with multiple pigmented naevi on the skin.[61] There were small pigmented nodules the size of millet seeds scattered along the course of the blood vessels of the pia mater and of the ependyma of the ventricles.

Generally at *post-mortem* examinations melanotic cancer has been found widely disseminated in the pia mater with multiple tumours, when it has not been possible to identify the actual starting point (Fig. 16). There has been a relative absence of signs, largely due, as in Babinski's case, to the growth not infiltrating but displacing the original tissues.[62] I exhibit specimens in which it was impossible to discover the seat of origin of the disease.

A woman, aged 36, had suffered vaguely in her head for four months. On admission to the Westminster Hospital a diagnosis of increased intracranial tension from multiple new growths was made. The patient was not relieved by decompression. The pia mater over the under surface of the medulla, pons, cerebellum,

and olfactory lobes presented a dark brown greenish staining. The cortex of the cerebrum, pons, and cerebellum under the pia mater exhibited numerous black nodules and spots. There were melanotic tumours in the base of the left lung, in the liver, in the retro-peritoneal tissue, and adherent to the outside of both suprarenal capsules, the substance of these organs being unaltered.

Melanotic Cancer in the Olfactory Mucous Membrane.

I have already stated that melanin pigment is of regular occurrence in the olfactory epithelium and in that of the labyrinth. Mr. de Santi has recently removed a melanotic cancer growing high up on the nasal septum, and the patient so far has no recurrence. The case is an extremely rare one. Mr. Arthur Cheatle has informed me that the occurrence of a melanotic growth in the labyrinth is not known to him.

CONCLUSION.

Experience incident to the removal of a large number of melanomas is similar to that in connexion with other varieties of new growths. Free and early excision is not followed by recurrence *in situ* except in malignant cases where the disease has already spread widely. Simultaneously with the change from melanoma to melanotic cancer there is a detachment and degeneration of cells producing metastasis which exhibits itself later on.

The general bearing of recent observations suggests the hope that further chemical research may arrive at a means of controlling the disease by therapeutic measures.

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DIFFICULT MIDWIFERY IN GENERAL PRACTICE.*

BY

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IN reading a paper and opening a discussion on such a comprehensive subject as difficult labour, I intend to limit myself to certain conditions and varieties of difficult labour which occur most frequently. In some of these the treatment has altered during recent years, and what was the accepted practice twenty years ago is now changed or considerably modified.

I would begin by emphasizing the fact that the importance of the obstetric branch of the art of medicine has of late been recognized in all the teaching schools. Less than twenty years ago the hospital student gleaned a few rudimentary facts from some small manual and proceeded to attend cases on the district with but a sketchy knowledge of the essential principles; the student of the present day attends the lying-in ward of his hospital day and night for a month before being allowed to attend cases on the district; and instead of an optional two months he is obliged to act as clinical clerk in the obstetric department for four months. Thus, by adequate instruction on normal cases and a considerable experience of abnormal cases, he comes to realize two very important things: first, the value of patience and the danger of interference in straightforward cases; and secondly, the importance of correct diagnosis in a difficult case so that the appropriate treatment may be carried out.

What the newly qualified doctor of the present day finds difficult is how to apply his hospital methods to general practice. For whereas in the hospital maternity ward time is no object, this is very far from being the case in private practice, and the doctor is found to be confronted at times with the problem of what is the best thing to do "in the circumstances." Sometimes forceps are applied before the suitable time has really arrived. In others, version has been performed. Sometimes all goes well, but at others the result is disastrous. The only real remedy lies in providing sufficient maternity beds in hospital in all towns for cases of difficult labour. Until such a time arrives I think it is fair to say that most doctors are to be congratulated on the skill and ingenuity displayed in conducting a busy midwifery practice. No doctor with surgical inclinations would dream of starting to remove an appendix in an ordinary bedroom, but there is no doubt that this is safer than many operations of difficult labour. In order to justify this assertion I would state that the mortality due to, and resulting from, childbirth is still very high for a "purely physiological" process, as it is termed.

The death rate per 1,000 births in 1920 was 4.1 (of which about 2.25 were directly due to abnormal labour, and 1.87 to puerperal sepsis of which the cause was often difficult labour).

Next, I will digress from the subject of my paper in order to speak about a theme of the greatest importance—namely, the prevention of difficult labour; and herein lies the most important advance in the practice of obstetrics.

The Prevention of Difficult Labour.

Ante-natal clinics have been formed and are still being formed all over the country, where the care of expectant mothers is carried on with great zeal. In the ante-natal clinic of to-day the pregnant woman is examined from time to time so as to exclude any possibility of difficult labour arising unforeseen. In noting the important points some such scheme as the following is used:

Scheme for Notes.

Age.
Date of last menstrual period.
Expected date of confinement.
Previous pregnancies or labours, with their character.
External Measurement: Interspinous. Intercristal.

* A paper read before the Dover and Folkestone Branch of the British Medical Association.