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# Melanin Pigmentation In Animals

*Donald Blaney\**

**T**HE CAUSES of coloration in animals is a problem that has occupied man's mind for centuries. That such is the case is certainly the result of the complexity of the problem, for it is not one which is easily solved and relegated to a place of minor importance. The color which we perceive is the net result of a myriad of inter-actions and contributing elements. Nervous control, hormones, environmental conditions such as temperature, light, and the color of the surrounding are but a few of the known factors affecting animal coloration. Perhaps the number of unknown factors far outweigh these.

The pigmentation problem, however, is not insurmountable, nor totally devoid of unity. In fact, all present evidence points to the existence of but one type of pigment-forming cell in the integument of fish, birds, man, and other vertebrates. This cell manufactures a substance known as melanin and is called, therefore a melanoblast. To propose that this cell alone is responsible for the extremely diverse coloration in various species or within a single species would seem to me presumptuous. It is probable, however, that this is not only the most important source of pigment in most species but also the only pigment cell common to so wide a variety of animals. It is true that pigments of other types occur in blood, the retina, the liver and other organs; but these pigments (hemoglobin, for ex-

ample) frequently serve some other, more important function while their color is merely incidental. Of all pigments, only melanin persists in a histological preparation. Any others, if present, are destroyed.

Because of the above facts—the wide distribution of melanin and its dominant role in determining coloration — this pigment alone will be treated extensively in the following pages. In order to discuss melanin with some degree of completeness, it was found convenient to divide the material into four topics. The first is concerned with the chemical reactions which lead to the synthesis of melanin and the various factors which affect its formation as far as these are known. This is followed by a section devoted to the discussion of the structural units or specialized pigment cells in the organism, their description, origin, and distribution. The third section is concerned with those animals that can change their color in response to the environment. While only a rather small percentage of the animal kingdom seems to possess this ability, it is not impossible that a study of this phenomenon may lead to a better understanding of pigmentation in more typical animals. The last section is devoted to abnormalities in the production and distribution of coloring matter in animals.

## **Chemical Formation of Melanin**

It is now an established fact that melanin can be formed from the amino acid tyrosine, and most investigators agree that the ultimate source of cutaneous pig-

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\* Mr. Blaney is a graduate student in biological chemistry and wrote this paper for a course in graduate veterinary physiology.

mentation in man and probably most of the lower animals is this amino acid. The original work that eventually led to these conclusions was begun in 1895 by Bourquelot and Bertrand (6). They recognized that a substance present in *Russula nigricans* was turned black by an enzyme in the same fungus. The substance was identified as tyrosine and the enzyme was given the name tyrosinase. It has since been found widely distributed in the vegetable kingdom and is present in many invertebrates. Recently there has been indirect evidence of tyrosinase in the vertebrates (9). The characteristic property of the enzyme is that in the presence of air it changes tyrosine solutions to red, reddish brown, and finally black. An insoluble pigment, melanin, is deposited.

Since the early work by Bourquelot and Bertrand (6) many theories have been proposed regarding the action of tyrosinase on the amino acid. These theories are composed of many chemical reactions involving such things as pH and ultraviolet light.

The melanin production picture is yet more complicated by the fact that injection of sex hormones may increase melanogenesis (10). Contrariwise, vitamin C, ascorbic acid, inhibits pigmentation of normal animal tissues when fed in excess (18). About all that is certain is that tyrosine is the precursor of melanin pigment.

#### The Melanin-containing Cells

It was formerly believed that any cell which contained pigment had produced it. Now it is well established that there are two cell types associated with cutaneous pigmentation. One produces melanin, these are called melanoblasts. The other contains but cannot manufacture it. These are the melanophores or chromatophores (14).

A typical melanoblast resembles other cells in several respects. It is provided with a cytoplasm enclosing a nucleus. The cell body is angular, and extending from the vertices of the angles are minute, threadlike branches. It is by means of these dendritic processes that the melanoblasts come into intimate contact with

the surrounding cells. The melanoblast is fragile and often spongy. The nuclei vary greatly in shape. They may be oval, spherical, notched, kidney-shaped, even double. The center of the melanoblast frequently contains "premelanin" granules. These are not darkly colored but become so by means of the dopa staining technique. It is only in the processes that melanotic maturation is complete. The granules, then, migrate from the center of the cell to the branches. From these branches the pigment is distributed to the other cell of importance in pigmentation, the melanophore. These are simply cells which, being in contact with the processes of the melanoblasts, have picked up the pigment and store it. This transfer has actually been observed in the case of pigmentation of the malpighian or germinal layer of the epidermis. Transfer to dermal melanophores, which also exist, has not been demonstrated, and, in fact, how this transfer is effected through the basal membrane is unknown.

From the foregoing discussion we may conclude that the melanoblast is a type of glandular cell. It elaborates and excretes its product. However, the product is a solid and insoluble. Furthermore, it is excreted neither directly externally nor into vessels, but rather into other cells. Because of this unique situation, Masson suggests the cells be called "cytocrines" in preference to endocrines or exocrines (14).

As was stated previously it was at one time believed that cells containing pigment produced it. To most investigators pigment seemed to appear in various parts of organisms without giving evidence of the place of origin. In 1934 and succeeding years experimental proof was presented to the effect that pigment cells, the melanoblasts, arise from the neural crest in amphibia, birds, and in the mouse (7,17). Such an origin makes readily understandable the distribution of melanin pigment. It is found in many structures of ectodermal origin such as the epidermis and hair, mucosal membrane, sensory organs, and so forth. There remains, however, some question as to the neural crest origin in man and in fact

many vertebrates. Indeed, the distribution of the pigment does vary somewhat in man and the lower vertebrates and invertebrates. In the lower forms the pigment occurs in the deeper parts of the body as well as in the skin. Weidenreich has pointed out that pigment "layers" can be noticed in many animal types (20). These are 1) a cutaneous layer which may be subdivided into dermal and epidermal; 2) a perineural layer around the central nervous system; 3) a pericoelomic layer around the peritoneum; 4) a perivascular layer about the blood vessels. In cyclostomes, fishes, amphibia, and reptiles, all of these layers may be present. In birds and mammals, deeper pigment layers are usually lacking or occur at best as "vestiges."

Some general statements can be made about the pigmentation in the cutaneous layer. As a rule, the pigment is more abundant in darker skins, but the parallelism does not always hold true. The darker or lighter shades of the pigment itself, the depth of location in the skin, and the colloidal or granular nature of the melanin particles contribute greatly in determining the hue of the skin. Melanin is seen mostly in the deep areas of malpighian or germinal layer, always in the basal layer of cells, often in upper layers. Small amounts are normally found as high as the *stratum corneum*, larger amounts after exposure to radiation. The melanoblast itself is always found connected to the basal membrane. Dendritic processes connect various melanoblasts with one another and project upward through the basal cell layer to the higher layers which in turn receive melanin from them. In areas of lighter pigmentation, the eyelids and palms for example, melanoblasts are less common but not absent.

Melanin pigment is also present in the corium. It is found only in superficial mesenchymal cells, usually in small amounts. It is quite regularly proportionate to the intensity of the neighboring epidermal pigmentation and is often lacking in the paler cutaneous regions. It is accepted by all that this pigment arises from the epidermal melanoblasts. How it crosses the basal membrane is unknown

since there are few if any dendritic processes that pass down from the melanoblasts. The pigment is transferred to reticulo-endothelial cells and eventually to the lymphatic nodes. It is doubtlessly gradually destroyed during the transit, for no increasing accumulation of it occurs normally in any part of the organism.

There has been no demonstration of a relation between melanoblast activity and the nervous system, except in the case of those animals that possess the ability to change their color rapidly. These will be treated briefly in the next section.

### Color Changes In Animals

While the ability to change color in response to environment is an attribute that is not universally distributed throughout the animal kingdom, it is found in a goodly number of species. Cephalopods, crustaceans, fishes, amphibians, and lizards have well developed pigmentary effector systems. Some investigators feel that facial blushing in humans is a vestige of a similar system.

When one begins to consider color change in animals, he generally thinks first of the chameleon. The common frog, however, can exhibit a similar, but slower, color response. If placed in a centimeter of water in a cool dark room and on a dark surface, a frog becomes intensely black in two days. In a dry vessel in a warm, brightly illuminated room, the same frog will assume a chrome or lemon color in two days. Brown, green, and other intermediate colors are seen in other situations (11).

How all this comes about has been explained to a certain extent as follows. In the integument of the animal exists a great number of pigment-bearing cells which are capable of altering their shape. When the animal is neither very dark nor light, the cells are of an irregular star-like or stellate configuration. When the animal is pale, the pigment granules within the cell are concentrated in minute aggregations, so that they tend to assume a small spherical contour. In the dark skin situation, the pigment is found

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diffusely spread throughout processes which almost appear to interlace with those of adjacent pigment cells forming a continuous network of black coloring matter.

Expansion and contraction of black melanin cells could produce only hues of black and various greys on a white background. Of course this alone would be inadequate to explain the array of colors that are at the disposal of the chameleon and the frog. There must exist other pigments in addition to the dark melanin, and granules that have a red or yellow color have been noticed. Whether these pigments are entirely unrelated to melanin, or whether they merely represent a stage in the oxidation of precursors to melanin or in the physical nature of the particles is a question that has not been settled. At present, evidence favors the latter viewpoint. At any rate, several such color systems of different tints probably exist side by side in the integument of the animal. Through alternate degrees of expansion and contraction of the various systems, it is conceivable that a wide variety of colors could be produced.

One immediately wonders how such a complicated system is controlled. Other effectors such as the muscles and glands have been shown to be under the control of nerves or hormones, and we might expect a similar control for the pigmentary effector system. It turns out that either, or both, the nerves and the hormones are involved in color response, depending on the animal in question. In the cephalopods the chromatophore has numerous radiating smooth-muscle fibres provided with nerves. The muscle fibres are attached at one end to the elastic envelope of the cell and at the other to some point in the adjacent tissue. When the nerves initiate a contraction of the muscle fibre the chromatophore is drawn into a thin, flat disk and the skin appears dark. In fish, histological studies have demonstrated that melanophores are under direct nerve control (2). Pouchet has shown, in addition, that when certain

nerves were cut, the chromatophores of the regions supplied by these nerves took on an intermediate tint and remained in this state (15). Later the actual location in the brain or the controlling center was determined. In fish thus far tested the color change depends upon the eye. Blinded fish show no response to the color of the environment. The possibility of double innervation of chromatophores, that is, by the sympathetics and parasympathetics, has neither been confirmed nor disproven.

In frogs the color response is principally under hormonal control. Hogben completely removed the pituitary gland from a number of amphibians, and the animals were left in a permanently pale condition (11). Examination of the skin showed that the melanophores were in maximum contraction. The injection of pituitary extract into these animals resulted in a temporary darkening due to the expansion of the melanophores. Nerve cutting experiments in the case of amphibia have largely yielded negative results.

As was mentioned in the preceding section, no relation has been established between the nervous system and the melanophores or melanoblasts in the higher vertebrates. Hormones, however, play some unknown role in the formation of melanin. During pregnancy, when there is an increase in hormonal circulation, an abnormal production of melanin, even to the extent of tumor formation, may occur. Additional malfunctions of the pigmentary system are discussed in the next section.

### Abnormalities

As is the case with most systems in any organism, a variety of abnormalities occur in the method of pigment production. These may be as insignificant as an absence of pigment in a small area where it is naturally expected or as dangerous as a melanotic tumor, some of which are as malignant as any known cancerous growth. These aberrations have been most extensively studied in man, but there is little reason to doubt that similar

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disorders occur in the lower forms.

Melanotic tumors may be benign or malignant. The simple benign type are commonly known as moles or nevi. They are particularly common in the white race, the average man having about twenty. The nevi result from an overactive melanoblast and are potentially subject to continued development to the state of a malignant melanoma. No statistical data seems to be available as to how often this occurs, but it is certainly infrequently since melanomas constitute only about one percent of all cancerous growths. Nevi on the feet and genitals are more likely to undergo malignant degeneration than a similar tumor in other parts of the body. The transformation frequently occurs with approaching puberty, and the opinion now exists that it is closely related to the endocrine system, notably the gonads and the suprarenal cortex. Malignant melanotic tumors may also appear during pregnancy. These are of a type of particularly rapid growth and are almost always fatal. In general, it may be said that fair or blond individuals are found more often to develop malignant melanomas; in Negroes the incidence is very low.

There is one well-known abnormality in man and other animals that is characterized by the name albinism. In total albinism no melanin is produced due most probably to a lack of some enzyme(s) in the transformation of tyrosine to the pigment. The hue of the skin, eyes, and other parts of the organism is principally a reflection of the red blood pigment, hemoglobin. Partial albinism may also occur. The lack of pigment in the skin and hair is limited to certain areas only. The eyes are usually pigmented.

Another deviation from normal pigmentation is called vitiligo. It is a case, like partial albinism, in which certain areas of the skin or hair lack pigment. It differs from albinism in that the affected area is usually more restricted and was at one time pigmented. Melaninogenesis can be initiated again in these areas by treatment with ultraviolet light

if the vitiligo has existed for only a short time. If several years have elapsed, the pigment cannot be restored. The malfunction is again attributed to the disappearance of some enzyme in the tyrosine reaction.

The effects of lentigo are the reverse of the above. An area, usually quite small, becomes hyperpigmented due to an internal unknown stimulus of the melanoblasts. In simple lentigo, this situation is harmless since the pigmented cells make their way to the upper layers of the skin and are sloughed off. The condition at this stage is in no way malignant, but it need not remain so. A disorder known as lentigo maligna seems to be a derivative of lentigo. Melanoblasts increase rapidly and migrate into the upper skin layers and also into the dermis. From the dermis they are cast off and metastasis occurs. Tumors begin in near and distant parts of the body.

Melanosis is a term used to define the case in which an organ is perfectly normal in every respect except that it is covered with, or contains, considerable amounts of melanin pigment. It occurs quite frequently in calves, usually in the form of black spots in the subcutaneous, subperitoneal, or intermuscular connective tissue. It seems to disappear in later life as it is very rare in adult cattle. Generalized melanoses, in which practically all of the internal organs are darkly pigmented has been noted in a male turkey and a domestic pig. External melanoses occurs occasionally in humans, and sometimes half of the body is black or dark blue. The individual is otherwise healthy.

The most recent report of abnormal pigmentation concerns a hyperpigmentation that developed during treatment of leukemia patients (21). Ten patients were given daily dosages of folic acid antagonists, and in seven of these, abnormal darkening of the skin occurred. Almost the entire body surface of one patient, who was kept alive nine months by the treatment, was dark brown before death. Examination of skin sections by the "dopaoxidase" activity method indicated true melanogenesis.

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Today somewhere between 40,000 and four million Americans have undulant fever, or brucellosis. Masquarading under the symptoms common to many other diseases, undulant fever appears sometimes to be anything from psychoneurosis to scarlet fever. No two cases act exactly alike. Thousands of cases go undetected, diagnosed as peptic ulcers, arthritis, or even typhoid. Brucellosis germs will cause infection in practically any part of the body.

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