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Cutaneous pigmentation: its formation and anomalies

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CUTANEOUS PIGMENTATION

Its Formation and Anomalies

Senior Thesis

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Omaha
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- It has been repeated many times, that of all the pathological processes occurring in the human body, the ones which are most convenient to observe and the easiest to obtain for histological study are those affecting the cutaneous structures. Notwithstanding, the older dermatologists classified diseases of the skin by their morphologic characteristics. This gave rise to a very accurate and detailed description of the various clinical conditions affecting the skin, but afforded little aid in understanding the processes underlying them. In modern dermatology, as in other special medical sciences today, effort must be made to establish the etiology and pathogenesis of disease by histopathologic, bacteriologic and physico-chemical methods. Only comparatively recently has enough accurate investigation been carried out to put the subject of cutaneous pigmentation on a satisfactory scientific basis. In many respects it is of academic interest rather than of practical value, although at times it is of great importance in diagnosis. The treatment, in general, is usually unsatisfactory as the condition is usually either permanent or tends to spontaneous involution by elimination through natural channels. However, since the processes of pigment formation, both from the physiological and pathological viewpoints, are so interesting and since such a multiplicity of cutaneous conditions can give rise to pigmentary changes, it is believed that a review of the subject is
worth while.

Another reason that a review of this subject is of value is in emphasizing the integral relation of dermatology to internal medicine. Dermatology emerged from internal medicine as a distinct specialty during the middle of the nineteenth century. The early dermatologists considered the skin to be an independent organ and its diseases peculiar to it. This was probably due to the idea that since the cellular pathology was limited to the skin the whole of the disease process was located there. It has been accepted by the dermatologists that the vast majority of the dermatoses are cutaneous manifestations of internal disorders. This change in view has been due to the realization of the importance in the production of the various dermatoses of such factors as allergy, intoxication, endocrine imbalance, faulty metabolism, immunity and resistance to infection, focal infections and even nervous defects.

Therefore, our purpose is to attempt to discuss pigment metabolism in relation to the skin—the income of pigment-forming material, the chemical formation of the pigment, its local disposition and finally its elimination. We shall also try to classify and discuss the various etiological factors that upset this metabolism so as to give rise to manifest changes in the cutaneous pigments.

In a review of this type covering such an extensive field with so many widely different conditions represented, a complete review of the literature is impossible. However,
in the discussion of each condition reference is usually made to the most complete and pertinent papers on that subject, most of which contain excellent bibliographies.
CLASSIFICATION

The anomalies of cutaneous pigmentation may be re-
viewed from several angles as to etiology, source and compo-
sition of the pigment, and the amount and distribution of
that present. Our classification seems to be satisfactory
as it takes all these into consideration as closely as poss-
ible. Probably the most fundamental characteristic of cutan-
eous pigment that must be observed is the source and compo-
sition of the pigment itself. Obviously, pigment of the skin
must either be of extraneous origin or be a true product of
body metabolism. Both of these types are found, the first
being relatively insignificant. Increased pigmentation of
the skin may be due either to an increase in the normal pig-
ment in the skin (melanin) or to the deposit of blood pig-
ments in the skin. It is clear that decreased pigmentation
can be due only to a decrease in the natural cutaneous pig-
ment. Therefore we will consider the etiologic factors of
cutaneous pigmentation under three general heads of exogenous,
 hematogenous and melanogenous pigments. There is a less well-
decribed group, the lipochromes, that will be mentioned.
I. EXOGENOUS PIGMENTATIONS

Pigments which are produced outside of the body may become manifest in the skin in two ways; that is, they may be directly introduced locally into the skin, or they may be absorbed and become secondarily deposited in the skin.

(a) Locally introduced pigments:

Probably the most commonly seen example of the first type is the ordinary tattoo. Tattooing consists of the introduction into the skin of insoluble colored substances which become encapsulated and thus form permanent stains. Microscopically, tattoo marks consist of relatively large particles of pigment, situated partly in the corium, but for its greater part in the subcutaneous connective tissues. Particles of pigment are also usually found in the neighboring lymph glands. The usual method is to outline the design, prick it either with one or a bundle of needles and then to rub in the pigments; or the pigments may be first applied and then introduced with an electrically vibrating needle. The pigments are usually carbon for blue or black, other pigments being cinnabar, carmine, indigo, Prussian blue, etc. (1).

Tattooing has probably been used since primitive times for ornamental and religious reasons. At present particularly in the white race it is seen little except in sailors. However, it does have some therapeutic uses. Filipo (2) describes a method of mixing of pigments and technic of application so as to correct such defects as
traumatic scars, X-ray scars, defects following such diseases as lupus, vitiligo, etc.

In the ordinary tattooing there is much danger of infection such as lymphangitis, erysipelas and pyoderma. Tuberculous infection has been reported (3). Keidel and Timmermann (4) quote many instances of syphilitic infection following tattooing. They also describe several cases in which the distribution of the syphiloderm were markedly influenced by the tattooing. Red tattoo, which is usually cinnabar (mercuric sulphide) seems definitely to inhibit the production of the lustic skin lesions in that area; while the black area shows a predilection for the eruption.

Gun powder stains, coal dust stains and similar stains produced by the accidental embedding in the skin of colored substances, usually carbon, are essentially similar to tattoo marks.

There have been reported a number of cases of cutaneous pigmentation of great diversity due to therapeutic uses of pigment-containing preparations. There are two cases reported due to a solution of ferrous sulphate used as a wet dressing in poison ivy dermatitis (5) (6). In Pucey's case the pigmentation was punctate in type and widely scattered, being demonstrable microscopically in the corium. Schamberg (7) reports a case of bluish pigmentation due to the injection outside the vein of an experimental gold proteinate being
used for the treatment of lupus erythematosus. Goekermann (8) reports fifteen cases in which a peculiar dirty black pigmentation of the face was due to a face cream which contained calomel. The granules could be seen microscopically. A similar case (8) has been reported in which the pigment was proven chemically to be mercury. The acid-base reaction of the skin seems probably a factor in this condition (8).

There is a condition known as blue atrophy of the skin which is often found in cocaine addicts. The name is descriptive, as there are scattered areas of thinning and depression of the skin, of varying shades of blue. Gottheil (10) is of the opinion that the pigment is an iron derivative due to the action of cocaine hydrochloride on the syringe and needle.

Maculae ceruleae are round, pea-sized, bluish-grey pigmented spots found on the abdomen and thighs in some individuals infested with pediculosis pubis, the crab louse. They are probably due to a pigment found in the louse near the salivary glands, which is probably introduced by the bite (11).

In all of these diverse cases of introduced pigment the pigment is usually granular, being demonstrable microscopically in most cases and is always in the corium or subcutaneous tissues. The treatment in most of these cases is unsatisfactory. The scattered granules may be removed mechanically, large areas may be excised with replacement by
grafts, or a destructive inflammatory process may be excited.

(b) **Ingested pigments:**

Pigmentation of the skin by ingested pigment is best exemplified by two conditions. Argyria or argyrosis is the permanent discoloration of the skin due to the prolonged administration of silver salts, usually the nitrate. The condition is becoming rarer as this chemical is no longer used in the treatment of epilepsy and gastric disorders as it once was. The hue of the affected skin varies from a bluish to a slate gray color, being more intense on the exposed surfaces. It is thought that the soluble salts are precipitated in the skin as the chloride which then undergoes darkening due to the effect of light. This accounts for the darker color of the exposed parts. However, the silver is found in all the tissues of the body. In all tissues, especially the skin, it shows a predilection for the elastic fibers. Localized argyria has been reported following silver arsphenamine (12), cautery of buccal leukoplakia with the nitrate stick (13) and the use of argyrol in urethritis (14). An excellent discussion of the subject with complete bibliography is given by Myers (15).

The condition of carotinemia which gives rise to a peculiar, yellowish, icteroid pigmentation of the skin was first described by Hess and Myers in 1919 (16), being due to the pigment carotin from a diet containing an excess of carrots. This yellowish discoloration of the skin has been
known in Japan as "aurantiasis cutis" of Baeltz since 1896, being due to the ingestion of large amounts of the Japanese orange "mikan" and squash (17). Its chief importance is to the internist in making a differential diagnosis of icterus. This condition has a predilection for the palms, soles and naso-labial folds and does not stain the sclera. The condition tends to clear up spontaneously when the intake of the pigment is lowered, as the pigment is in the cells of the stratum corneum.

Although workers in modern industry are showing large amounts of dermatitis from contact with the various chemicals, few of these chemicals cause direct pigmentary changes (13). Many of these such as trinitrotoluene cause a local staining of the hands due to a direct contact. In the later stages the general yellowish discoloration which is sometimes present is probably due to hemolysis and toxic hepatitis (17).

II. HEMATOGENOUS PIGMENTATION

Pigmentation of the skin arising from the blood pigments may be divided into two general types: the deposit of blood pigments due to localized hemorrhages which may be caused by either local factors as trauma or to a general condition as in some of the blood dyscrasias; and secondly, to some general disorders causing red cell break-down with
deposit of pigment secondarily in the skin. In any case, the presence of blood pigments free in the cutaneous structures may be considered an abnormal condition. Although the vascular naevi produce a marked discoloration of the skin, they will not be considered here as the blood is present as such within the lumen of vessels.

(a) Physiology:

The processes involved in the metabolism of the hematogenous pigments are quite complicated and on many points are still controversial. The following summary of only the most important points which are generally accepted is all that is necessary for our purposes (16)(20)(21)(22)(23)(24)

The source of all the blood pigments is a very complex, iron-containing substance, hematin, which is usually found in the body in union with a protein, globin, forming hemoglobin, the red, oxygen-carrying substance of the erythrocyte. After a life of from fifteen to thirty days, the red cell is broken down probably in the spleen by phagocytosis. The liberated hemoglobin either directly or after further break down in the spleen is absorbed by the liver where first the iron is freed. Much of the iron is retained, being utilized by the bone marrow in forming more hemoglobin, while the excess is excreted probably through the intestine. From the remaining iron-free substances, a pigment, bilirubin is produced by the action of the Kupfer cells and is excreted in
the bile, by the liver cells. This substance gives fresh bile its golden yellow color but on oxidation it gives rise to biliverdin which gives the greenish cast to old bile.

From bacterial action in the intestine bilirubin is reduced to stercobilin which gives the normal feces their brown color. Urobilin, the pigment of the urine, is either formed from stercobilin after reabsorption or directly in the liver from bilirubin. Although the chief source of the bile pigments is hemoglobin, according to Whipple (23) the amount of bile pigment is not quantitatively related to hemoglobin destruction as some bile pigment is formed directly from ingested food. He also thinks that some bilirubin may be formed in other tissues than the liver, probably the reticulo-endothelial system.

After an extravasation of blood into tissue the process of the break-down by hemoglobin is somewhat different. The hematin breaks up into a reddish-brown, iron-free pigment hematoidin, and a yellowish, iron-containing pigment hemosiderin. Hematoidin, believed to be identical with bilirubin, is found in the greatest amount in large hemorrhages, especially in the interior of the mass, as in hemorrhage into the body cavities and in large hemorrhagic infarcts, where the cells forming it have died and disappeared. Hemosiderin, the more important, is probably not a true pigment but merely a mixture of closely related pigments. It usually can be seen microscopically as brown granules which give the
chemical reactions of iron.

It has been shown that although most of the bilirubin is formed in the liver by the action of the endothelial Kupfer cells, some may be formed at other points in the body, probably also by endothelial cells. Therefore, the local break-down of hematin is analogous to the processes in the liver, as hematoidin, identical with bilirubin, is formed, by action of the local endothelial cells, absorbed and finally excreted by the liver cell. The hemosiderin formed locally, however, tends to remain as such for long periods of time because of its relative insolubility.

(b) Local hematogenous pigment:

Direct trauma is probably the usual cause of local extravasation of blood into the derma and subcutaneous tissues. The commonest example of this is the bruise or "black and blue spot" which shows the usual color changes of the absorption of subcutaneous hemorrhage. The color of fresh, whole blood subcutaneously is bluish-black. Following this there may be a reddish cast due to the presence of the hematoidin, but by far the commonest color is a greenish-blue due to the presence of both the yellow hemosiderin and the blue whole blood. This greenish color gives way to the brown of the hemosiderin which gradually fades through the shades of yellow until absorbed. Actual wounds of traumatic origin also may give rise to a discoloration of the scar from blood pigments after healing. Insect bites are also another form
of trauma that may cause subcutaneous hemorrhage with discoloration, purpura pulicosa.

In the involution of many of the lesions of the more common skin conditions, blood pigment may remain. Some of these are erythema multiforme, erythema nodosum, tuberculosis cutis, particularly erythema induratum, the syphilodermes and various other lesions in which local extravasation may take place.

There are several dermatoses due to local changes in the smaller vessels of the derma that give rise to varying amounts of subcutaneous hemorrhage and resulting pigmentation. The most common type of pigmentary change secondary to pathology of the vessels is that caused by eczema hemostatica. In this condition due usually to varicose veins, there is stasis, edema and inflammation with some diapedesis of red cells resulting in pigmentation. In some cases the pigments may be of melanotic origin due to the inflammation (25).

Purpura annularis telangiectodes (Majocchi) is a rare disease which has been very carefully studied by MacKee (36). It consists of a progressive disease of several months duration with a bilateral distribution limited to the extremities. The lesion is at first a red macula consisting of dilated capillaries with some dark red hemorrhagic punctae. The lesion spreads peripherally tending to form annular lesions with pigmentary changes in the center. The lesion tends to spontaneous involution leaving a pale brown pigmented spot.
Pathologically the condition is an obliterating endarteritis with aneurismal sacculation, the rupture of which gives the hemorrhage. The causative factor is unknown.

Poikiloderma atrophicum vasculare is an atrophy of the skin preceded by an inflammatory stage with telangiectases, capillary hemorrhage and pigmentation of blood origin. It is symmetrically distributed over the majority of the body surface. Beginning in early adult life, it is slowly progressive to the atrophic stage. Its cause is unknown. It is a very rare disease, there being only sixteen cases reported in the literature, only two of which are in this country (27).

Idiopathic multiple hemorrhagic sarcoma of the skin (Kaposi) occurs as numerous symmetrical plum-colored to purplish tumors varying in size from a pea to a walnut, usually found on the extremities. The earlier lesion may be an ill-defined infiltrated patch with an increase in pigmentation. Pathologically, the lesion appears to be proliferation of capillaries accompanied by hemorrhage and the capillaries tend to become cavernous. There is a heavy deposit of hemosiderin and a sarcomatous change in the surrounding connective tissue probably that of the vessel wall. Opinion as to the true nature of the condition vary. Kaposi originally thought it to be a true sarcoma of relative low malignancy, possible an angio-sarcoma (28). Others take it to be a primarily chronic inflammatory change with a tendency to become secondarily sarcomatous (29).
Dorffel in the latest work on the subject after careful histological study concludes that, "The sarcoma of Kaposi is a disease of the reticulo-endothelial system, including a disturbance in the monocytogenic function which at times may terminate in true malignancy" (30). He also believes that hemorrhage with deposit of pigment and proliferation of the vessel wall cells are the initial pathologic changes. Clinically at this time the lesion is a faint, hemorrhagic macula. It is also a rare condition.

Schamberg (30a) described a condition as a peculiar progressive pigmentary disease of the skin which has since been called by his name. It begins as pinhead red points usually on the lower extremity in young males. These tend to disappear spontaneously, leaving a dark reddish-brown pigmentation. There is a tendency to progression with increasing areas of hyperpigmentation. Histologically there is perivascular infiltration and a pigmentation which has proven to be hemosiderin (30b). There are changes in the lining and walls of the vessels so it is assumed that the pigments arise from red cells that found their way into the tissues by diapedesis through a diseased vessel wall. This disease is not so rare as the literature would indicate.

The diseases of the blood and blood-forming organs are another condition that often gives rise to subcutaneous hemorrhage. These are known as the purpuras, although strictly speaking, the term is applied to any lesion characterized by hemorrhage into the skin. With the fading of the lesion
some pigment remains in a bruise. They are chiefly medical conditions with the purpura considered as merely symptomatic. The following classification is modified from Pusey (31) and Christian (32):

1. Symptomatic purpura.
   a. Infections as seen occasionally in pyemia, septicemia and malignant endocarditis, and in specific infections as in typhus, and occasionally in measles, scarlet fever, smallpox, cerebrospinal fever, syphilis and malaria.
   b. Toxic, as from venomous snake bites, and from various medicines as copaiba, quinine, belladonna, mercury, ergot and the iodides.
   c. Cachectic such as is seen in cancer, tuberculosis, Bright's disease and the debility of old age.
   d. Neurotic, occasionally seen in tabes, acute myelitis, and the severe neuralgias. They may follow severe emotional disturbances and rarely with hysteria.
   e. Mechanical, as from traumatisms or from venous stasis produced by paroxysms of coughing or epileptic attacks.
   f. Familial purpura in several members of the same family has been observed — a condition related to hemophilia which also may cause subcutaneous hemorrhage.
   g. Purpura simplex — mild cases usually tending to disappear spontaneously in a few weeks accompanied by no other symptoms.
   h. Avitaminosis, as in scurvy.

2. Arthritic, or better anaphylactoid purpura, including the purpura rheumatica of Schonlein and Henoch's purpura. These are usually accompanied by arthritis, abdominal colic and urticaria, and are believed to be allergic in origin.

3. Thrombocytopenic purpuras.
   a. Essential thrombocytopenic purpura (purpura hemorrhagica, morbus maculosus Werlhofii). This is a tendency to hemorrhage into the skin and mucous membranes characterized by a reduced platelet count, a prolonged bleeding time and a non-retractile clot. There also seems to be an increased permeability of the capillaries.
   b. Secondary thrombocytopenic purpura.
      (1) In blood diseases, as leucemia, aplastic and pernicious anemia and agranulocytosis.
      (2) In some of the symptomatic purpuras enumerated above as the infectious and toxic the purpura may or may not be due to platelet destruction.
(c) **General hematogenous pigment:**

In the second general class of hematogenous pigmentation instead of a local break-down of red cells, the pigment is formed elsewhere and secondarily deposited in the skin. This usually occurs in diseases of the blood with excessive red cell destruction and in various disorders of the biliary system.

Any disorder of the blood-forming organs leading to an excessive break-down in the red cell will give rise to a generalized discoloration of the skin. This is commonly seen in the typical lemon yellow color of the skin occurring in pernicious anemia (33). The discoloration is due to a deposit of hemosiderin (34). A similar condition is seen in aplastic anemia and following the absorption of a large mass of blood after a hemorrhage into a body cavity.

In many cases of chlorosis there is a peculiar greenish hue, particularly around the eyes and chin, although there is no excessive red cell destruction. The color is probably due to iron pigments the bone marrow is unable to utilize properly (35).

In discoloration of the skin due to biliary disease the most common type is icterus or jaundice which may be due to many causes. It is brought about by an excess of bilirubin in the blood giving rise to a diffuse pigmentation of the skin, conjunctivae and mucus membranes. The excess of bilirubin in the blood is brought about by three mechanisms. The three types of icterus are; first hemolytic, caused by an
increased break-down of red cells due to fragility of the cell, giving rise to an excess of bilirubin in the blood. This might better be classified as resulting from changes in the blood rather than a disturbance of the liver. Secondly, we have the hepatogenous type resulting from inability of the liver cells to secrete the bilirubin already formed, as in acute yellow atrophy, infectious cholangitis and toxic hepatitis. Thirdly, we have the most common form, obstructive jaundice, due to obstruction in the flow of bile in the bile ducts or capillaries by such conditions as stone in the common duct and cirrhosis, and resultant reabsorption, of bilirubin (36). The dermatologist is particularly interested in the intense pruritis that is often seen in cases of severe jaundice. The so called "blue reaction of Brugsch" is also of interest to the dermatologist. It consists of the intradermal injection of a small amount of one percent solution of potassium ferricyanide. A bluish discoloration indicates the presence of bilirubin and is therefore of use in differentiating bilirubin pigmentation from those due to melanin or hemosiderin (37).

Although we have discussed hematogenous pigmentation from several angles, none of the anomalies have been due to an actual disorder of the metabolism of iron. Hemachromatosis is a disease arising from the inability of the body to properly utilize iron with retention in the tissues of iron-containing pigments, chiefly hemosiderin, but there is some
melanin also (39). The pigmentation occurs as a patchy, grayish-brown area irregular in outline and distributed chiefly on the exposed parts and around the skin folds, nipples and genitalia. However, all the tissues of the body show a marked deposit of hemosiderin granules. It is always accompanied by a cirrhosis of the liver which may be secondary to the irritation of the hemosiderin deposits or may be a primary factor in causing the metabolic disorder. In the last stages it is usually a diabetes mellitus from which the name of bronze diabetes is derived. The diabetes is probably due to an accompanying cirrhosis of the pancreas arising from the irritation of the hemosiderin granules. The increase in melanin may be due to the deposit of hemosiderin in the adrenals, comparable to Addison's disease or to a local irritative action in the skin of the pigment (39). Mallory (40) believes that the condition is due to chronic copper poisoning with union of the copper with iron substances giving rise to their retention in the tissues. He has reproduced the lesion in several species of animals. In clinical cases, he notes that often they give a history of occupational exposure to copper or are users of alcoholic liquors in which copper can be often demonstrated.

Even though the blood pigments are a common and important source of cutaneous pigmentation, we may conclude that most of the conditions in which they are found are of interest chiefly to the internist. There are a few interest-
ing though rare conditions of hematogenous pigmentation which are primarily dermatologic. However, the dermatologist should be familiar with the other types from the standpoint of problems in differential diagnosis.

III. MELANOGENOUS PIGMENTATIONS.

The anomalies of pigmentation arising from melanin differ from the previously discussed, as melanin occurs normally in the skin, being formed through metabolic activity of specialized cells. Cells that do not normally form melanin can not acquire this power under pathological conditions, the normal process merely being stimulated to a higher degree of activity. The lack of pigment in the skin is merely a failure of this process to function normally. Therefore, the process of normal melanogenesis is the first thing to consider in a discussion of melanotic pigmentation.

(a) Melanogenesis:

Until recently melanin was thought to be formed from hemoglobin, but largely through the work of Bloch (41), this has been disproven. At present there is little difference of opinion as to the fundamental process. An excellent review of the subject of melanogenesis is that of Percival and Stewart (42) from which the following summary is adopted with modification from other authorities.
Melanin is found in the skin and its appendages where it shows wide individual and racial differences, and in the single individual differs widely with varying physiological and pathological stimuli. Besides the skin, it is found in the eye occurring in the retina, choroid, ciliary body and iris and in the substantia nigra and meninges of the nervous system. The coloring power of melanin is very great, the entire skin of a negro containing only about one gram of melanin (43).

In white, human skin melanin appears as light yellow to brownish granules in the cells of the basal layer of the epidermis, and also in a few cells of the adjacent prickle layer. Melanin containing cells exist side by side with melanin free cells and except for the pigment, are identical. The pigmented basal cells are most numerous on the sides of the rete pegs. Some of the basal pigmented cells possessing dendritic processes are seen occasionally. Their significance will be discussed later. The melanin granules are uniform in size, tending to concentrate towards the upper surface of the cell, forming a cap over the nucleus. The pigment content is greatest in the epidermis of the nipple, axilla, scrotum and anus. In the dark races, all the cells of the basal layer and deeper strata of the rete malpighii contain pigment which becomes less as they approach the stratum granulosum. The granules differ only in number and distribution.

Throughout the dermis, branched melanin containing
cells are normally found. In addition there are scattered melanin granules lying free between the connective tissue bundles. The melanin granules within these cells are coarse and irregular in contrast with the fine uniform granules of the epidermal cells.

The pigment of the hair is contained in the matrix and bulb as dendritic cells and in the shaft as coarse granules within and between the cells of the cortex.

The exact chemical composition of melanin is not known as it has never been isolated in the pure state. It is thought to be a group of nitrogenous substances which contain neither iron nor sulphur as an essential part of the molecule, but contain various amino acids and the indole ring.

It has been shown that melanin production can occur in portions of epidermis which have been cut off from the general circulation and in Thiersch grafts in vitro (44). This shows that the final synthesis of melanin from its precursor is a specific function of cellular activity. This problem can be divided into two parts; the nature and source of the precursor, the chromogen, and the means by which the living cells produce melanin from it.

As early as 1902 it was known that an amino acid, tyrosine would act as a chromogen in certain plants and cold-blooded animals, supposedly by the action of the enzyme tyrosinase. The tyrosine-tyrosinase reaction could not be proven to exist in warm-blooded animals. In cases of generalized
melanoma, an excess of ortho-dihydroxy-benzene or catechol is excreted in the urine. In Addison's disease with a dysfunction of the adrenals there is an excess of melanin produced. Therefore, Block assumed that the precursor was related to tyrosine but had two hydroxyl groups attached to adjacent carbons as in catechol and adrenaline. He tested, 3,4-dihydroxyphenylalanine, shortened to "dopa" by use of initial letters, and found it gave rise to melanin. The chemical relation of the above substances is as follows:

\[
\begin{align*}
\text{Catechol} & \quad \text{Adrenaline} & \quad \text{Tyrosine} & \quad 3,4-\text{Dihydroxyphenylalanine} \\
\text{Dopa} & \quad \text{Dopa} & \quad \text{Dopa} & \quad \text{Dopa}
\end{align*}
\]

Sections of skin soaked in a solution of dopa under appropriate conditions showed deposit of melanin in just those positions in which melanin formation normally occurs. The amount of this response to dopa corresponded with the known capacity of the skin for melanin formation. Extracts of normal skin incubated with dopa show production of melanin. Control solutions as well as extracts of albino skin gave negative results. Therefore, melanin was formed from dopa only in those places capable of pigment formation. Block tested a
large number of chemically related substances and found that none of these produced melanin as did dopa. Therefore, he concluded that dopa was not only a precursor of melanin but that the reaction was highly specific. It has been recently proven that 3,4-dihydroxyphenylalanine is present as an intermediary product in the tyrosin-tyrosinase reactions (45). However, this was after the discovery of the dopa reaction by Bloch. If melanin is formed from tyrosine then it must undergo the first stage of oxidation to dopa elsewhere than in the melanoblasts.

The power of the skin to produce melanin is destroyed by heat, low concentrations of cyanide and delicate changes in pH. From these facts and because of the high degree of specificity, Bloch concluded that the dopa reaction depended on the presence of a melanin-forming enzyme, dopa oxidase.

Not only has the dopa reaction explained the formation of melanin but has given us an extremely useful tool for the microscopic study of melanin-containing cells. When frozen sections of skin are left in contact with a solution of dopa under appropriate conditions, certain cells of the epidermis and hair follicles become darkened, which is due to a deposition of fine, brown granules in the cell cytoplasm. This constitutes a positive dopa reaction and is indistinguishable microscopically from normal melanin pigmentation. If the reaction is strongly positive, the whole cell cytoplasm
is a diffuse black and the granules are masked. The intensity of the reaction coincides with the existing degree of pigmentation. In other words, a close parallelism exists between the natural pigmentation (actual or potential) of a skin and its capacity to oxidize dopa. Thus it seems as if the reaction is identical or at least closely allied to normal melanogenesis and indicates the presence of melanin-producing enzyme, dopa oxidase.

The fact that the darkening is confined to the cytoplasm is evidence that the nucleus does not immediately participate in melanin formation as was once thought. The presence or absence of the dopa reaction does not necessarily mean that the individual cell is permanently in that condition but the condition may probably be merely a transitory physiological state.

Melanin-containing cells may be either dopa positive or dopa negative. The dopa positive cells are assumed to contain dopa oxidase and are capable of producing melanin. These cells are known as melanoblasts or pigment formers. The dopa negative cells, even though they contain melanin are considered to be incapable of producing melanin. They contain no dopa oxidase. Their contained melanin is produced by the melanoblasts and comes to lie in the cell by a process of phagocytosis. Therefore these cells are known as melanophores, chromatophores or pigment carriers.

The epidermal melanoblasts are morphologically of
two types. The one is identical with the adjacent basal cells except for its pigment and the other possesses dendrites. Recently the dendritic cell has been closely studied in relation to pigment formation by Becker (46) and Peck (47). The dendritic cells are situated in the basal layer in contact with the basal cells but in highly pigmented skins may be found in the lower layers of the prickle layer. The cell body is usually slightly larger than the basal cell, with narrow branching dendrites extending laterally and upwards. They have never been proven to extend into the derma and the general opinion is that they are limited to the epidermal layer. Becker found dendritic cells in all regions of the cutaneous surface and in the mucous membranes of the mouth and pharynx, concluding that they are a normal constituent of the epidermis.

There are three possible theories as to the origin of the dendritic cells: 1. Every basal cell is dendritic, but only a few are identified as such by their contained pigment. 2. Dendritic cells and non-dendritic cells are genetically different types. It was originally thought the dendritic cell was identical with the Langerhans cell which is now known to be of nervous origin. The structural appearance has suggested that the pigment is formed in this cell and distributed to the other epidermal cells. Pautier (48) has suggested that the cell is part of a syncytial system to distribute nutritive material and chromogen to the epidermis from the vessels of the dermis and to carry off the wastes
and formed pigment. However, no connection of these cells with the dermis has been proven although at times artefacts make it appear as if some of the dendrites extend into the dermis. 3. The non-dendritic cell changes to the dendritic form on functional stimulation. At present the accepted function of the dendritic cell is pigment formation. They usually contain pigment and in poorly pigmented areas as the mucous membranes, may be the only cells that do so. They all give a positive dopa reaction at the time of pigment formation. The number of dendritic cells increases with increased pigment formation and decreases with the lessening of the pigment-building activity. During these periods a number of transition cells may be seen (47). At the height of melanin formation nearly all melanoblasts are dendritic (49). These facts seem to point to the fact that the dendritic cell is merely a basal cell in a high state of its functional activity which is pigment formation.

The branched pigmented cells of the dermis are always dopa negative and may be regarded as chromatophores which are incapable of pigment formation. Miescher (50), by injecting melanin into the dermis showed that the introduced pigment is phagocytized by the connective tissue cells which are then indistinguishable from the normal chromatophores. It would appear as if the chromatophores receive their pigment from the cells of the epidermis. However, true dopa positive melanoblasts are found in many animals and in the
human in two conditions, Mongolian spot and blue naevus, both of which will be discussed later. This brings up the question of the mesodermal origin of the melanoblasts with subsequent migration to the epidermis. Peck (49) in a study of the rabbit embryo concludes that the positive dopa reaction is the first evidence of melanin formation and this is always in the epidermis. The melanoblasts that seemed to lie in the dermis were part of the hair follicles.

The pigment containing cells of the hair matrix and bulb give a positive dopa reaction while the pigmented cells of the shaft and papilla are dopa negative. In the retina during embryonic life, the pigmented cells are dopa positive, but when full development is reached they become dopa negative and are assumed to have lost their power to form pigment. In addition to melanoblasts, the leucocytes are capable of oxidizing dopa because they contain a polyphenolase. This is a non-specific reaction.

Formed melanin is removed from the epidermis by two routes. The bulk of the melanin is carried upwards towards the surface as the cells move away from the basal membrane, finally to be desquamated with the cells of the stratum corneum. Some finds its way into the dermis where it is ultimately phagocytosed and carried away in the lymph system.

In the lower animals melanin has wider function than in the human as variations in color, both pigmental and structural, play an important part in the preservation and
propagation of the species. Some of the lower forms are able to alter their coloring very rapidly by means of contractile chromatophores. In man, however, the chief function of the skin as a whole seems to be protective. The pigment seems to enter into this function by protecting the underlying tissues from the injurious effects of the actinic rays of the solar spectrum as shown by the tanning effect of ultra-violet light and generalized pigmentation of the races living near the equator. The morphological distribution of the melanin as a cap over the nucleus suggests a protective function. It has been proven that a solution of melanin absorbs almost completely the lower end of the spectrum (51). Pillat (52) has shown that in Chinese with vitamin A deficiency and disease of the conjunctiva, there is a hyperpigmentation of the conjunctiva. He assumes that this is a protective function as the diseased conjunctiva is hypersensitive to light.

All of the factors controlling melanogenesis are not known. Obviously the inherited racial factor and the amount of exposure are probably the two most important factors. The influence of the endocrines on pigmentation is of great importance but the mechanism is not at all well understood. It is known that various endocrine dysfunctions markedly affect pigment production. This will be more fully discussed later. Block thinks that a local alkalinity aids pigment formation.

Therefore, we can conclude that our evidence tends
to show that the dopa reaction very closely resembles the natural process of melanin production. That is, melanoblasts contain a specific enzyme, dopa oxidase, which acts on a specific chromogen, 3,4-dihydroxyphenylalanine, to form melanin. We can also conclude that these melanoblasts occur usually in the epidermis, the functional form being the dendritic cell, and are of ectodermal origin.

(b) Melanotic Hyperpigmentations:

Any theory of melanin formation must explain satisfactorily the appearance of the melanin in the pathologic hyperpigmentations due to melanin. These conditions, classified as follows as to etiology, can usually be explained on Block's theory.

(1) Congenital: As the hereditary factor is one of the most important in controlling the amount of cutaneous pigment, it seems logical at this point to discuss the factors that give rise to the normal color of the skin. These are four in number: First, the capillaries of the skin which is shown best by the blushing and blanching that so often accompany vasomotor instability; second, the amount of subcutaneous fat; third, the thickness of the granular layer of the epidermis - if thick as on the palms and soles the skin appears white, if absent as on the lips it appears red; fourth, the amount and distribution of the melanin granules. (52)(53). The last is probably the most important and of most interest to us. "The ascending scale of morphological conditions
parallelizing a progressively deepening grade of pigmentation may be described as follows: (a) Few cells of basal layer pigmented with few granules - blondes; (b) More cells containing more granules - brunettes; (c) A more or less complete basal layer of cells with many melanin granules - mulattos; (d) The cells of the basal layer packed and distended with pigment granules, the cells of the more superficial layer also with many granules. (54). In most skins there is a slight yellowish cast. The light reflected from the deeper tissues passes through the melanin granules and emerges at the surface with a yellow component. Presumably the granules absorb the complementary blue. In any case their effect is not only to darken the skin but also to add enough yellow to produce brown in heavily pigmented skins. In lighter skins, the yellow component is not so obvious. Whenever the epidermis is unpigmented and closely packed melanin granules appear in the corium, bluish or grayish effects are to be expected. This effect is seen best in such conditions of heavy corium pigmentation as Mongolian spot and blue naevi. It also probably accounts for the blue of maculae ceruleae and blue atrophy already discussed (55).

As mentioned previously Mongolian spot (sacral patch, "Mongol fleck", "taches bleues") is an instance of true mesodermal melanoblasts. It is found in the newborn of all Japanese or Mongolian stock. It is also often seen in the Negro. It is usually found as a well defined blue patch over the sacrum and consists histologically of many dopa
positive cells closely packed in the corium. Mesodermal melanoblasts are present in some of the higher apes, giving the skin a bluish tint. This sacral patch is thought to be an evidence of the descent of man from the apes. It was assumed that the spot was limited to the highly pigmented races and that they were therefore closer to the apes. The incensed Japanese finally proved that the sacral patch could occur in any race. Lately with the dopa reaction it has been shown that all infants have these mesodermal melanoblasts, the difference between the white and Mongolian being only a matter of degree (41). They tend to disappear spontaneously with the disappearance of the mesodermal melanoblasts and the increase in epidermal pigment.

Other congenital hyperpigmentations that are of interest are the nevi which will be discussed under neoplasms, and lentigo (freckles, ephelides) which will be discussed under physical factors.

(2) Physical: Physical energy of several kinds may cause hyperpigmentation, the most common being specific wavelengths of radiation. When discussing the function of melanin, we showed some evidence for believing that the function of melanin was for protection from the actinic rays of the solar spectrum. If this is so then increased radiation should increase the amount of pigmentation. This reaction is the common sun tan. The first evidence of overexposure to the sun's rays is a painful erythema which in severe cases may be accompanied by general symptoms, such as fever. After
several days desquamation occurs with gradual increasing pigmentation. The inflammatory reaction is due to absorption of ultra-violet light in the skin. The hyperpigmentation is not due to the inflammatory reaction as it has been shown that the two reactions are caused by different wave lengths (56). It is assumed that this hyperpigmentation is due to a local increase in the oxidation of the chromogen. How light initiates this reaction is not known. There are four factors governing the extent of this reaction: First, the capability of the individual skin to react to the radiation; second, the presence of the specific pigment producing radiations in either sun light or substitutes; third, length of exposure; and fourth, the distance from the source (52A).

The relationship of sun tan to helio-therapy is interesting as it has been noted that people who do not tan readily do not respond well to helio-therapy. It is possible that a chemical change induced in the epidermal cells by the radiation is the common cause of the hyperpigmentation and the beneficial effects of exposure to ultra-violet light (56).

Of particular interest to the dermatologist is the sensitization of the skin to the sun's rays or its substitutes. It has been shown that a dermatitis with resulting heavy hyperpigmentation often follows exposure to the sun following applications of perfume. The changes are localized to the areas to which the perfume was applied, usually the neck or ears. It has been shown that the substance in the
The perfume responsible is oil of Bergamot. However, in the absence of light there is no reaction. This is known as Berlock dermatitis (57)(58). This principle has been used in some of the sun tan creams. The same type of reaction can be caused by ingestion of the sensitizing substance. Weider (58) in discussing occupational melanosis which is found in workers handling coal tar products, suggests that the melanosis is due to sensitization to light by the coal tar product, as the hyperpigmentation occurs usually on the exposed parts. He also discusses the condition that existed in Germany during the war known as "the war melanosis of Riehl". This is generally believed to be due to sensitization to light but there is a difference on whether tar is the offending factor or some substance in the changed dietary.

Means by which a sensitizer acts is not known but it is probably either by allowing more complete absorption of the pigment production fraction in the radiation or by changing non-pigment producing fractions into those that do (51). It is probable that this is the mechanism in many of our other cases of hyperpigmentation.

Lentigo or freckles may best be considered to be due to some localized congenital defect of unknown origin that causes hyperpigmentation when exposed to light.

The reactions to the radiation of X-ray and radium are very similar to that of light. However, these are of much shorter wave length and tend more for production of
inflammation and less toward the production of pigment. However, after a slight erythema there is a hyperpigmentation. This reaction is shown very well by the work of Peck (47) in studying experimentally the reaction of the skin to thorium-X, a radium derivative.

Heat will produce an erythema that is followed by hyperpigmentation. Erythema ab igne is usually reticulate in type and found on those areas continually exposed to heat as on the legs of stokers. Cases due to continued use of a hot-water bottle and to exposure to heat of a stove have been reported (60).

Continued trauma will produce hyperpigmentation, probably an evidence of reaction of the skin to continued irritation. The term chloasma is applied to patches of hyperpigmentation of the skin. The idiopathic variety is due to external irritation as from the rubbing of a brace, friction of a garter, irritation from drugs and the like.

A related condition is the so-called mal vagabondi found in tramps who have been exposed to poor hygiene over long periods. It is due in some measure to dirt, but more to the irritation arising from infestation with pediculosis corporis, from the irritation of the beast itself plus scratching. It usually consists of scattered irregular areas, light brown in color, but may become general and very dark in cases of long standing. Any intense pruritis with long continued scratching may cause hyperpigmentation.
The so-called sailor's and farmer's skin is a condition of hyperpigmentation and hyperkeratosis due to continued exposure to sunlight and the elements over a long period.

A case of generalized mottled hyperpigmentation following an electric shock has been reported. The pigment was not fixed but changed with the sympathetic nervous system (61).

(3) General Conditions: Hyperpigmentation may be secondary to many diseases of the body that are not primarily diseases of the skin. One of the most interesting of these conditions as well as the most difficult is the pigmentary changes accompanying endocrine dysfunction. Any analysis of these conditions is made more complex when it is remembered that the individual glands can hardly be considered individually, but as interrelated in function.

Addison's disease of the adrenals gives rise to a definite hyperpigmentation. The pathology is usually a tuberculous involvement of both adrenals but may be due to a neoplastic or luetic process. Besides pigment there is also a marked asthenia, low blood pressure and gastro-intestinal symptoms. Histologically the skin is normal except for a marked deposit of melanin both in the epidermis and dermis (38). Although there is much pigment, the dopa reaction is weak and there are few dendritic cells. We have explained the close chemical relationship between dopa and adrenaline.
Block's theory is that with the disease of the adrenals, there is a diminution in the amount of adrenalin produced with an excess of its precursor circulating in the blood. This substance is taken up by the epidermal cells and from it the cells are able to form melanin. The weak dopa reaction shows that although there is much pigment following a continued reaction, little dopa oxidase is left in the cell (42). Another explanation that was given before the dopa theory was known was sympathetic stimulation.

It has long been known that hyperpigmentation accompanies pregnancy. In fact the process was considered physiological. The hyperpigmentation of the areola was an important sign in the diagnosis of early pregnancy. Chloasma uterinum also often accompanies pregnancy. It is also found in organic and functional utero-ovarian disorders. From the obvious relationships of these disorders to pregnancy and ovarian disorders, it was thought that these changes were due to ovarian dysfunction. It has become to be accepted that the functions of the ovary and the pituitary are closely related, from experiments in the endocrine cycle of the female. Most of the experimental work on relationship of pituitary and pigment have been done on the melanophores of the amphibians. These show that hypophysectomy causes albinism in the tadpole due to a lessened number of pigmented cells in the epidermis with fewer granules to the cell (62). Similar results followed experiments with the pineal (63).
Much of the work has been done on the effect of pituitary extracts on the color changes of amphibians. This is due to a stimulation of the chromatophore with contraction of the cell, and is not a true production of pigment (64). From the evidence chiefly clinical, we must assume that there is a definite relation of the secretion of the ovary and the hypophysis to the production of pigment. The method is not known although the mechanism must be a localized stimulation of the melanoblasts directly by an increase of secretion, as Becker (46) found an increase in the dendritic cells of the areola of the nipple in pregnancy. Although there is no evidence for it, action of the secretion on the sympathetic nervous system has been suggested.

In thyroid disease increased pigment formation may be seen. Murray (65) reports hyperpigmentation in 22 of 120 cases of exophthalmic goitre. There is usually a diffuse pigmentation most marked over the face, neck and hands. This may be especially marked on the eyelids. In some cases, chloasmatic spots are present. Krantz and Means (66) report six cases of hyperpigmentation accompanying myxedema. In these cases the pigmentation was patchy and usually distributed on the face and arms but other parts of the body were involved. It clears rapidly with the administration of thyroid. It seems queer that hyperpigmentation can occur in two such different conditions. The mechanism in both types is unknown although the distribution on the exposed surfaces in
both conditions suggest sensitization to light. The sympathetic has again been blamed.

Thus practically all the endocrines have been implicated in pigment formation. The only one for which there is a logical explanation based on observed facts is Addison's disease. In the other types the sympathetic is said to be chiefly at fault but there is little evidence for this. There may be a localized stimulation through other means. In any case the relationship of the endocrines to pigmentation is largely unknown.

There are two intoxications that often cause pigmentary changes. The fact that the ingestion of small doses of arsenic over long periods of time will give rise to a hyperpigmentation has been known for a long time. It may occur in any shade of brown with some mottling. It is quite generally distributed having been reported in the mucous membranes (67). It is commonly accompanied by hyperkeratosis of the palms and soles which are predisposed to malignant degeneration. It is due to the administration of quintavalent compounds such as Fowler's solution. It tends to disappear spontaneously. Hyperpigmentations have been reported following exfoliative dermatitis due to the trivalent compounds, as arephensamine, which was probably due to the inflammatory reaction rather than to the arsenic (68)(69). In Ronchese's case the areas of a previous rossola were free from hyperpigmentation. Osborne has carefully examined histologically
by special methods the tissues from arsenical hyperpigmentation (70). He finds a large number of small granules of arsenic chiefly in the epidermis, some probably intracellular. He concludes that indirectly, either by mechanical irritation of the cell or action on the precursor, melanin was formed. He also found (71) that in trivalent arsenic the granules were localized around the vessels of the corium. He concludes that trivalent arsenic has a predilection for mesodermal structures and quintivalent for ectodermal.

With the increased use of phenolphthalein in proprietary laxatives, there has been noted a fixed eruption that often accompanies prolonged ingestion of phenolphthalein. The eruption consists of a few scattered, irregularly grouped, non-elevated patches varying from pink or bright red to purple. They tend to persist more or less indefinitely and eventually produce a persistent yellowish to dark brown pigmentation. On further ingestion, they tend to recur usually at the sites of the former lesions. Antipyrin sometimes may produce a similar eruption (72).

The role of the nervous system in the production of pigment is very uncertain. As stated above the sympathetic has been blamed for the cases associated with endocrine disturbance. The close relationship of the adrenal with sympathetics has long been recognized. In the case from electric shock the shift in pigment was believed due to the sympathetic. Ellermann (73) states that pigmentary anomalies, with an increase and a decrease may be due to nervous diseases, as
epidemic encephalitis, cerebral arteriosclerosis, tabes, paresis, syringomyelia, infantile hemiplegia, etc. Also certain mental affections may cause some change in pigment. He believes these changes due to a viscero-cutaneous reflex and reports three cases to illustrate this.

Ochronosis (74) is a true disorder of the metabolism of the phenol compounds in which melanin is produced. There is a very diffuse pigmentation, particularly of the cartilages, tendons, sclerotics and skin. The pigmentation of the skin is greatest over the face and in the axilla probably due to the excretion of melanin in the sweat. There is usually some joint involvement and the urine is usually dark, from alcapton or melanin. It is usually due to a congenital defect in the metabolism of the phenol derivatives which could probably form a dopa-like compound. In 11 of the 41 cases reported by Oppenheimer and Kline (75) there had been a prolonged external use of phenol with a probably intoxication.

Various authorities (76)(77)(9) have listed a great variety of internal diseases that may cause pigmentary changes. Other than this listing there is not any attempt to discuss or explain these conditions of pigmentation. The following have been said to produce hyperpigmentation: abdominal tumors, tuberculosis, particularly of the peritoneum, chronic peptic ulcer with dilatation, cirrhosis of the liver, carcinoma, arteriosclerosis, chronic heart disease, chronic infections, rheumatoid arthritis and malaria. It may well be that, if there is such a mechanism as a viscero-cutaneous
reflex that stimulates pigment production, it is the mechanism at work in these cases.

(4) Dermatoses: Hyperpigmentation is extremely common in the various skin diseases. It is particularly liable to be found in the inflammatory diseases. It is commonly seen as one of the last evidences of an involuting lesion. The dopa reaction is frequently lost in areas of skin inflammation, indicating a temporary loss of pigment function, or rather a diminution of the ferment activity. Following this period the reaction becomes strongly positive and may be associated with hyperpigmentation (42). The reason for this is not known but it is possibly due to an interference with the cell metabolism with a later compensatory overactivity or due to a direct stimulation of the cell by the products of the inflammation. In all of the inflammatory lesions the process is similar and a late stage in the development of the lesion. Therefore, since the pigmentation is usually not a striking part of the clinical picture, we think that listing these conditions is sufficient. In some conditions pigmentary changes are nearly always associated with the clearing lesion. These are lichen planus, dermatitis herpetiformis (Duhring) and most cases of psoriasis. In pellagra, the eruption recurring in the same areas gives rise to a marked hyperpigmentation. In these cases it is well to tell the patient that as the lesion clears, there will be a discoloration as there is a tendency to blame this on the treatment. There is a
large number of other inflammatory conditions in which pig-
mentation may be present according to the severity of the
process and the ability of the patient's skin to react.
Among these are, lepra, the papular syphiloderm, eczema,
dermatitis venenata and exfoliativa, pityriasis rosea, var-
ious types of pyoderma, erythema multiforme particularly
the iris type, lupus vulgaris, the various tuberculides, lupus
erythematosus particularly the disseminated, herpes zoster,
pemphigus and mycosis fungoides. Practically speaking any
of the inflammatory dermatosis may give pigmentary changes.

There are several dermatosis in which the pigmen-
tation is such a prominent feature in the clinical picture of
the disease that they must be commented on more fully than
was necessary for the inflammatory conditions.

The only one of the conditions that is basically
inflammatory is urticaria pigmentosa. It is characterized
by the development of wheals which tend to subside and reform
in the same area. With the repeated occurrence pigmented
lesions form at the site of the wheal, which is probably due
to the continued irritation. It usually begins during the
first few months of life and disappears after several years,
but may persist. The pigment increase is chiefly basal with
the presence of many mast cells in the corium. The disease
is quite rare (78)(79).

Xeroderma pigmentosa is a rare type of atrophy in
which the skin undergoes the most extreme changes of senile
atrophy in a few years. They usually begin in early life with
scattered areas of erythema. These are followed by abundant freckling, being large and prominent. They are exaggerated by exposure to sunlight, becoming worse with each summer. The skin becomes dry and harsh with atrophic, pitted spots and telangiectases. Keratoses develop which tend to become malignant. The eruption is much worse on the exposed parts, so it is probably a congenital defect of the skin which consists largely of a susceptibility to light (80). Becker shows that the pigmentation is due to a large amount of epidermal pigment (81).

Another rare hypertrophy is acanthosis nigricans. The lesions are warty papillomatous growths of dirty brown to black color. The whole of remaining skin may be thickened with hyperpigmentation. The lesions show a predilection for the face and neck, axilla, inguinal region and deep folds of the skin. Histologically there is marked thickening of the cornified and the prickle layers with marked increase of pigment, both epidermal and dermal. There are two types, the malignant in which there is usually visceral neoplasms and the benign or juvenile. In the malignant it is supposed to be due to pressure on the sympathetic and the juvenile to hypoadrenal function as was shown by Weider's case (82).

Another hypertrophy, the diffuse type of scleroderma is often accompanied by hyperpigmentation. In large symmetrical areas, the skin becomes very indurated, thickened and rigid. The borders of the patches merge gradually into the normal skin. The patches are often hyperpigmented. Hist-
logically the only change in the epidermis is hyperpigmentation. In the corium there are perivascular infiltration and marked increase of the connective tissue elements. Little is known of the etiology except that it is probably an endocrine disturbance (83).

Fibroma molluscum (Von Recklinghausen) are multiple subcutaneous tumors of varying size and number (84). At first there is a gradual increase in size and number of the lesions but later this becomes fixed. Pathologically they are neurofibromata arising from the connective tissue of the nerve trunks. The skin over the tumor shows a marked tendency to become hyperpigmented. The most interesting fact from this angle however, is that the hyperpigmentation may occur long before there is any evidence of the tumor. In Little's case (85) the pigmentation was present at birth but the tumors were not noticeable until the age of ten. It is possible that the pigmentation is due to nerve involvement in these cases.

Carate is a disease endemic in certain hot, damp portions of tropical America. It is a local disease of the skin particularly the exposed parts. The characteristic pigmentary changes are dark to black patches. There is some tendency to stippling, associated with the pigmented areas with which there are areas of complete depigmentation. It sometimes has a branny scale and at times some itching is present. Histologically the stippled areas showed an increase
of dermal melanophores with an interruption of the basal melanoblasts. In the diffuse blue areas there is a large number of chromatophores. In the depigmented areas, there were no pigment in either epidermis or corium. Associated with the pigment changes were vacuolation of the rete, and absence of elastic tissue. The process would seem to be at first an increased formation of pigment with a removal by the corium and finally lack of pigment formation. The blue color is caused by the dermal pigment as has been explained. The etiology is unknown (86).

_Tinea versicolor_ (pityriasis versicolor) is a fungus disease produced by the microsporon furfur. It consists of small patches of various size with a fine branny scale. These may coalesce to form large irregular areas. It is usually located on the chest or back, but cases on the face have been reported (87). The localization to the covered parts is thought to be due to the inhibitory effect of the sun on the fungus (88). However, Castellani (89) states that in the tropical varieties it is commonly found on the face which he thinks is a related disease, _tinea flava_. The usual color is a dirty yellowish or brown but in the tropics a black variety is known. In negroes the patch is usually lighter in color. Strictly speaking the condition should not be classified as a true pigmentary change as the color is in the fungus itself. However, as it so closely resembles a true pigmentation, it is included for differential reasons.
There is a class of cases in which there are merely scattered irregular areas of hyperpigmentation resembling large freckles, in which no other change either generally or locally can be found. The majority of chloasma (liver spots) have no demonstrable etiology. These may be localized sensitization to light or be due to endocrine or sympathetic dysfunction.

(5) Neoplasms: Pigmented nevi or melanomata (moles) are really congenital defects but as a disease process may better be considered under the tumors. We will not attempt to discuss their relationship as tumors to dermatology and medicine as it has been done very thoroughly by Dawson (92) and earlier by Johnston (93). We will attempt to discuss the melanomas as to their relation to our knowledge of the process of pigment production.

The pigmented cells in the melanomas are true melanoblasts as shown by the fact that they are dopa positive. The source of the melanoblasts give rise to two general types of melanomas, the epidermal and the dermal. Becker (94) has studied the melanoma from the standpoint of melanoblasts.

The epidermal type is the ordinary mole which is probably one of the commonest of all skin lesions. They are all fundamentally the same and clinically may be classified as the macular (nevus spilus), the nodular, the warty (verruccous), papillary, linear and diffuse or giant. Any of these
may have an excess of hair (nevus pilosus). They are more frequent on the face, neck and back (82, p. 589).

Histologically the above types have the same general picture. They contain the characteristic nevus cell, arranged in columns or groups in the corium. The clinical varieties are due to the arrangement of the cell groups from differently shaped projections. With the larger nevi the lowest cells tend to atrophy with a fibrosis that may extend to the surface. The overlying epidermis may be quite pigmented, containing many dendritic cells, some of which lie at the epidermal-dermal juncture. Some of the nevus cells are also dopa positive (82, p. 542)(84).

The problem which this picture presents is the origin of the nevus cells. It has been thought that they represent endothelial cells arising from the lining of lymph or blood vessels, connective tissue cells (chromatophores). (82, p. 666-669). There is some evidence that they might be derived from the sheath cells of Swann (85). These have been abandoned for the theory of epidermal origin. It is thought that some of the basal cells undergo alteration and descend into the dermis during embryonal life. By proliferation they form the groups of nevus cells, epidermal cell arrests. Therefore they are closely related to the epidermal-dermal juncture cell mentioned above.

We have mentioned previously that besides Mongolian spot, true mesodermal melanoblasts are found in the blue nevi (Jadassohn). Clinically they are non-elevated, circumscribed
and appear deep blue. Histologically the epidermis is usually unchanged while in the corium are large numbers of elongated pigmented cells coursing parallel to the collagen bundles. These cells are in a sharply circumscribed area, tending to be massed around the follicles, gland ducts and vessels (84).

Both of these types of nevi tend at times to become malignant, the incidence being larger in the mesodermal type. This probably is due to the fact that it is a less differentiated cell.

Clinically, any nevus that has remained stationary for a number of years, and then begins to enlarge with increased vascularity and pigmentation should be considered malignant. It may not reach any size, but will break down and ulcerate with frequent hemorrhages. There is a tendency to early metastasis first to the regional lymph glands, then to the liver. This early metastasis is due to the lack of cohesion between the cells (84). There is usually a definite history of trauma to a benign nevus as the application of caustics, incomplete removal or continued mechanical irritation. However, melanoma may arise from trauma without a preceding nevus.

In the epidermal nevus the question arises of the origin of the malignant cells. Formerly, the nevus cell was thought to be the point at which the malignant change started. However, at the present, the dendritic cell in the epidermo-dermal junction seems to be the sole offender (84). These
cells extend downward from the epidermo-dermal margin into the groups of nevus cells exciting secondary malignant change in the nevus cell (92, p. 659). In the periphery of an infiltrating mass of cells, are always found many dendritic cells indicating the probable origin of the malignant cell from the epidermal dendritic cell. The actual process is increase of activity of these cells without hyperpigmentation, then increase in number of melanoblastic cells with hyperpigmentation and finally disintegration of the epidermal cell structure and penetration of the melanoblasts into the deeper structures. These infiltrating cells are always dopa positive whether they contain pigment granules or not. The line of advancing infiltration always extends much further than the clinical border. This shows the necessity for wide excision of these tumors for after excision the trauma stimulates the remaining cells to much faster growth. These tumors in all cases are melanocarcinomas as both the epidermal and nevus cells are of ectodermal origin.

The process in the blue nevi is practically the same except the origin is certainly the mesodermal melanoblasts. In this case the tumors are true melanosarcomas.

Becker (94) describes lentigo maligna, a macular hyperpigmented lesion found in old people from which some authorities say the majority of the melanocarcinomas arise.

The question of the relationship of the pigment to the malignant change is interesting (92, p. 512). It has been suggested that the pigment makes the cell unstable and
more susceptible to trauma. The pigment itself may act as a chronic irritation in initiating a malignant change. The pigment may merely be an indication of the accelerated activity of the cell.

(c) Depigmentations:

Depigmentary changes are caused by the lack of melanin as it is the only natural pigment in the skin. The loss of the ability of the cells to form pigment is shown by the negative dopa reaction.

The congenital absence of pigment or rather, the ability to form pigment is known as albinism. It may be partial, occurring as patches of whitish or pinkish skin present at birth. In complete albinos, the skin is abnormally white, and pinkish where very vascular. There is no tanning on exposure to sunlight. The hair is silky and white. From absence of pigment in the eye, the pupils are red and the iris pink, with photophobia from excess of light. The defect is probably hereditary (96).

The most important depigmentation is the condition known as vitiligo. The only changes are those produced by the disturbance in the formation of pigment. There is no alteration in sensation and no other structural changes in the skin. The hair on the patch also usually loses its pigment. The border may be hyperpigmented so that the patches stand out in greater contrast. The patches are usually multiple and tend to a rough symmetry, showing predilection for
the face, neck, back, hands and arms. They vary in size from small spots to large patches. A case of complete depigmentation in a negro has been reported (97). The course is extremely slow, the patches tending to spread with the addition of new ones. It is more common in the pigmented races, probably because it is easier to recognize. The depigmentation is permanent as the cells have lost the ability to form pigment as shown by the negative dopa reaction in the spot with a strongly positive reaction around the edge. It is usually stated that vitiligo patches do not have the power to form pigment when stimulated with ultra-violet light. However, With (98) found on strong stimulation a macular, freckle-like pigmentation occurred, spreading from the periphery to the center with the patches becoming more visible due to pigmentation of the surrounding skin. Kissmeyer (99) in studying these macules with dopa found that most of these cells were dendritic. He concludes like Block that vitiligo is due to an exhaustion of the dopa oxidase with loss of pigment forming power. Some of these cells on strong stimulation may regain some of this power. With also found that at first the vitiligo areas reacted very strongly to the ultra-violet. However, gradually they acquired a tolerance even though there was no evidence of pigment formation. He concludes therefore that the organism has some other protective mechanism against light than melanin. This may be either a compensatory mechanism due to the absence of melanin or may be the primary mechanism the hyperpigmentation being an accompanying phenomenon. The
etiology of this condition is unknown but it appears as if it might be a nervous condition (73).

A symptomatic leucoderma resembling vitiligo patches may be secondary to many dermatoses (100). This is most often seen in syphilis and due to its tendency to localization on the neck has been called a "collar of pearls". These leucodermic spots seem to follow a roseola and occupy the same areas as the macula. The papular syphiloderm as stated, forms a hyperpigmentation. Psoriasis also at times causes a true leucoderma although in treated cases the stimulation of the treatment causes a hyperpigmentation of the surrounding skin while the patch which was protected by the scab remains white. A leucoderma has at times followed a para-psoriasis, eczema and pityriasis rosea (100). In these conditions the leucoderma is temporary probably due to local toxic action on the epidermal cells. The depigmented areas of carato have been described (5b). In morpha or circumscribed scleroderma there are scattered ivory, infiltrated patches. However, this is not a true leucoderma as it is not primarily a pigment disturbance (101). In a scar whether traumatic or following a disease process the newly-formed epidermis is so altered so as to lose its power to form pigment resulting in the common white scar.

A condition resembling a leucoderma in that it is an irregular white area with some tendency to form groups is nevus anemicus. It is due to a congenital lack of blood ves-
sels in the corium. It can be differentiated by inability to show hyperemia (102).

Achromia parasitaearia is a condition, the mechanism of which is in dispute. After certain of the fungus diseases most of which are quite superficial there are often noted leuodermic areas. Kistiaikowsky (88) believes that the fungi acting as a filter screens the patch from the sun, preventing sun tan. In contrast to the tanned surrounding skin, the patch appears white. The French (103) think the color is due to the light color of the fungi, an atypical form of tinea versicolor. Pardo-Castello (104) states that it is a true leuoderm as it is found on shielded parts, is seen in negroes, and tends to persist, in one of his cases as long as eight years. The power of forming pigment is not lost, as with strong stimulation the color returns. Leuodermic areas following pityriasis rosea due to protective action from the sun have been reported (105).

IV. LIPOCHROMES

Although unimportant from the dermatologic standpoint, these are included for the sake of completeness.

The lipochromes are yellow pigments highly fatsoluble. They normally occur in the chromaffin system, and corpus luteum. They are the pigments found in brown atrophy of the heart. The character of these pigments is not known but probably they are a group of closely related pigments.
resembling carotene, which has been discussed in carotinemia. The metabolism of their formation is absolutely unknown. It is quite possible that they are of exogenous origin, being carotin-like substances. After ingestion, since they are so highly fat-soluble they tend to localize where there is a large amount of fat. At present it is believed that there is a close relation between carotene and vitamin A, but this does not concern us here.

Any dermatosis in which there is localized fatty infiltration can give rise to yellow plaques. The one disease in which this is most evident is xanthoma (106). Xanthoma planum is a fairly common disease occurring in the form of rectangular, chamois, yellow patches embedded in the corium. They are somewhat irregular in outline and are slightly elevated. The epidermis is normal and there is no induration. The color is usually chamois yellow but may vary from a white to dark brown. The lesion begins as pinhead-sized lesions, gradually increasing in size to pea-sized. They are practically always limited to the eyelids. They sometimes are found on the rest of the face. Xanthoma multiplex are nodular instead of flat but otherwise are like xanthoma planum. The nodules are from pinhead sized to hazel nut. The lesions are usually numerous with some tendency to localize on the hands and feet, elbows and the buttocks.

Xanthoma diabeticorum is always associated with diabetes mellitus. In this case the eruption begins as inflam-
inflammatory papules of dull red color. The fatty degeneration of xanthoma occurs first in the tops of most of the lesions. They are usually located on the buttocks, elbows and knees. Unlike the other forms there is some itching.

Histologically the first change noted is the presence of the characteristic "foam cell" in the region of a blood vessel. These are large pale vacuolated cells, containing fat. There may be some free fat in the tissues. As the foam cells increase, there is a fibroblastic reaction. The fibrous reaction increases so that old lesions appear as fibromata.

There is nearly always a hypercholesterolemia in these cases and it is fairly well proven that the condition is a derangement of lipoid metabolism (107)(108). The fat is phagocytosed in the endothelial cell with a secondary fibrosis. The yellow color being due to the presence of lipochromes in the fat.

There are two other extremely rare conditions that produce yellow xanthoma-like papules. These are colloid degeneration of the skin (colloid milium) and pseudo xanthoma elasticum, a degeneration of the elastic tissue. In both cases the color is probably due to lipochromes.
CONCLUSION

In this paper the metabolism of the pigments that may give rise to manifest changes in the skin were discussed. Particular attention was paid to the formation of melanin, the natural pigment of the skin. Our present state of knowledge of melanogenesis is due almost entirely to the work of Bruno Bloch with the dopa reaction. There seems to us to be a striking omission in the literature of the dopa reaction. It is well proven that dopa when applied in vitro to cells capable of producing melanin will form melanin in proportion to the power to form pigment. To our knowledge no attempt has been made to produce melanin in vivo by the injection in a living organism of dopa, the supposed precursor of melanin.

We have discussed briefly some one hundred and twelve entities that may give rise to anomalies of pigmentation. These have been collected from the literature by us as in no place were we able to find a nearly complete compilation of these conditions.

These conditions were classified as to type of pigment and etiologic factors. The classification is largely our own.
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