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REVIEW

Inappropriate Use of Albino Animals as Models in Research[1,2]

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CREEL, D. *Inappropriate use of albino animals as models in research.* PHARMAC. BIOCHEM. BEHAV. 12(6) 969–977, 1980.—Sensory-neural, biochemical-metabolic, and physiological anomalies occur in albino mammals. There are ontogenic and biochemical parallels between the senses, peripheral nervous system, endocrine glands, metabolism, and melanin pigmentation. All albino mammals examined have abnormal optic systems. Many drugs cannot be adequately evaluated in an albino model because of melanin's ability to bind and interact with some chemicals. There is evidence that a general reduction in melanin pigment is correlated with a paucity of amino acids necessary for normal chemical function of the brain. There is a high probability that enzyme levels indicative of metabolic performance are deficient in the liver and kidneys of albinos. Congenital defects are associated with hypopigmentation in animal models and human syndromes. Melanin is found in abundance in the eye, inner ear, and midbrain where neural impulses are initiated indicating a possible role as an electrophysiologic mechanism. Microwave irradiation differentially affects albino and pigmented animals. Implications of these observations and other reports of anomalies associated with hypopigmentation suggest caution in the use of albino and other hypomelanotic animals as normal models in biological research.

Albinism Catecholamines Melanin Tyrosinase Tyrosine

IN biological and behavioral research concern is frequently expressed for the selection of appropriate animal models. How much one may generalize from findings depends upon the model selected in both obvious and subtle ways. Guinea pigs require exogenous vitamin C; rats do not. Salamanders regenerate appendages; mice do not. Nonetheless, a defect in methodology has become a part of biological science: the majority of experiments using mammalian animal models are being conducted with albino animals. I assert that albino animals are anomalous and nonrepresentative. This assertion is based on the premise that melanin and the metabolic roles of its precursors affect a number of developmental and biochemical systems. Evidence supporting this argument will be reviewed in the following discussion.

Clues to the existence of anomalies in hypopigmented mammals have existed for over a century. Darwin noted that many white cats with blue eyes are deaf [27]. In 1934 McCrady summarized that reduced size of optic nerve, thickness of occipital cortex, and diameter of oculomotor fibers may be effects of the albino gene [88]; and in 1942 Bruesch and Arey reported fewer optic tract fibers in albino as compared to pigmented rats [13]. A substantial body of evidence has accumulated to suggest relationships between melanin pigment and the metabolic pathways of its precursors with biochemical, developmental, physiological, and sensory-neural systems (see Fig. 1).

BACKGROUND

Melanin pigment is widely dispersed in nature and has survived millions of years of selective evolution. This suggests that it has very basic functions. Species that lack pigment have contributed little to evolution except those cases of organisms living in nearly complete darkness. From an evolutionary point of view one of the least representative animals would be that lacking melanin pigmentation.

Hypopigmentation is principally the result of two mechanisms. The albino has a normal distribution of melanocytes, the melanin producing cells, but because of one of several biochemical defects, such as lack of active tyrosinase, the albino is unable to synthesize melanin pigment. White spotting is due to the absence of melanocytes, and an all-white animal lacking melanocytes is by definition considered all one spot. There are many genes associated with forms of hypopigmentation. *C* is the gene controlling tyrosinase, the enzyme that promotes the oxidation of tyrosine to form melanin pigment. It is present in all pigmented mammals. The albino is the result of the least active allele at the *c* locus albino series. There are many other genes that produce spotting or significantly reduced pigmentation, including dominant white (W), splotch (Sp), microphthalmia (mi), spotting (*s*), pink-eye (*p*), dilute (d), and buff (bf). On the one hand it is important to distinguish between albinism, *per se*, and other forms of hypopigmentation; on the other hand it is

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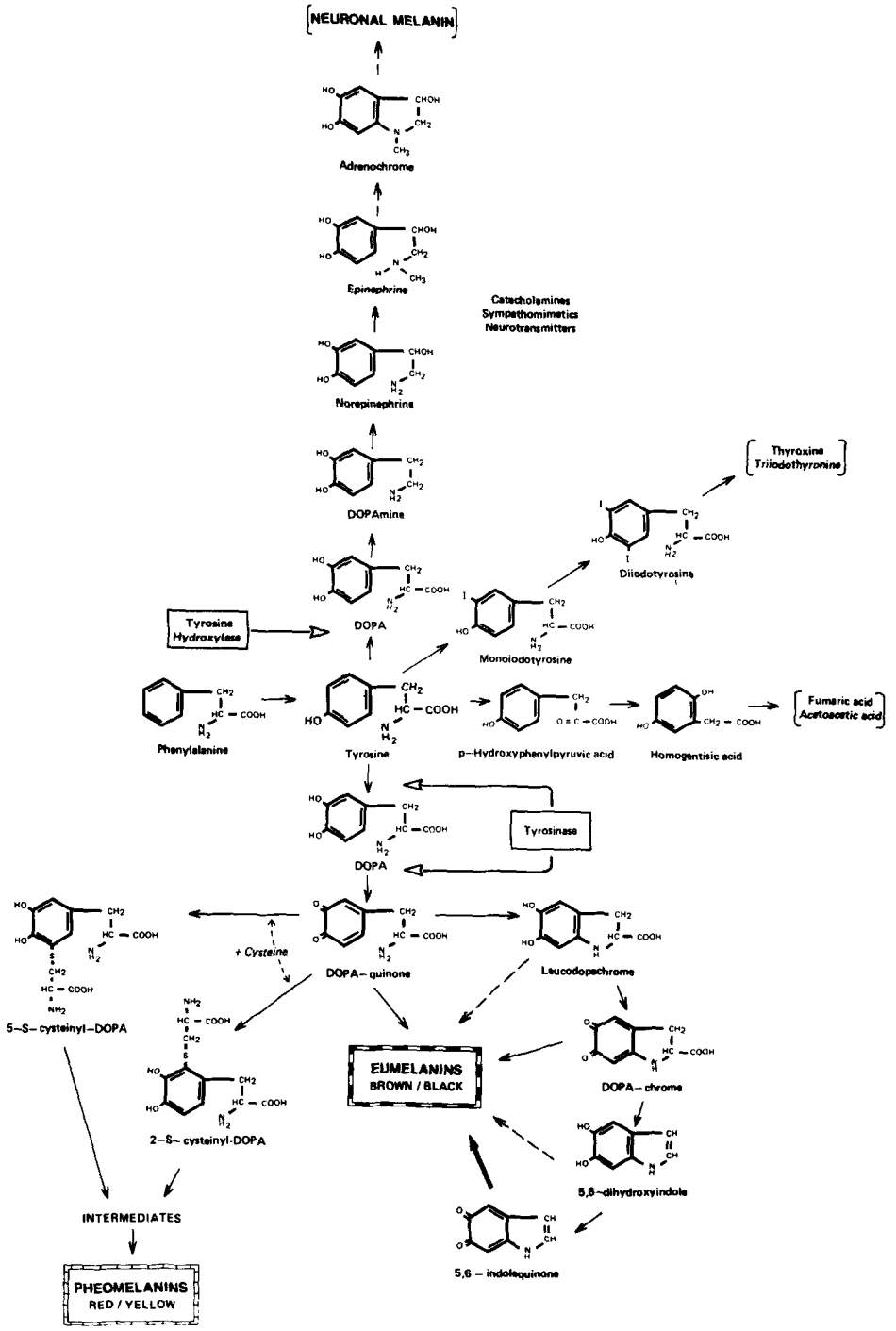

FIG. 1. Metabolic pathways of melanin and related pathways of tyrosine in the liver, brain, adrenal medulla and thyroid.

important to be aware of the recurrent similarities of effects of various forms of hypopigmentation.

The use of albinos in research is an historical accident, the exemplar being the rat. The albino rat is a domesticated variation of the Norway rat, *Rattus norvegicus* [107]. During the 19th century albino forms of *Rattus norvegicus* were perpetuated by animal fanciers for show purposes. From these collections came laboratory strains. Donaldson began using them at the University of Chicago in 1893. Donaldson's albino rat colony was also the origin of the strain at the Wistar Institute. In 1924, Donaldson published *The Rat*, in which he emphasized physiological similarities between rat and man [32]. Subsequently the albino rat and albinos of other species were adopted for use throughout biological research.

Why use the albino? A prevalent argument is that albinos

are nonaggressive. The paradox is that albinism *per se* is not associated with docility. The apparent docility of albinos is associated with a nonagouti gene and independent docility polygenes. Most strains of albino rats and mice are carriers of a recessive pigment modifying allele nonagouti (*a*) that is not expressed. The normal wild type agouti (*A*) produces a pigment pattern characterized by a band of yellow near the tip of each hair. Nonagouti (*aa*) hairs lack the band. When hairs lack the subterminal bands they become uniformly black. The modifying allele nonagouti (*a*) is not expressed because the albino mutation (*cc*) prevents the expression of coat color. It is *nonagouti* that is associated with docility [65–67, 107]. Black rats, for example, are as nonaggressive as nonagouti albino rats. On the other hand, albino rats from an agouti strain are reported to be as vicious as captive wild rats; when dropped many would attack laboratory personnel trying to retrieve them [66].

There are many genes affected by domestication. The effects of gene pools altered during domestication is a related, but not critical, issue defensible from opposing points of view, including questioning the validity of the supporting data [10,75]. Although it is sometimes difficult to separate effects of hypopigmentation from effects of other genes there are sufficient data available from several scientific disciplines which makes this possible.

I shall discuss the *direct* association between hypopigmentation and biologic anomalies affecting: (1) sensory-neural anatomy and physiology, (2) biochemistry and metabolism, and (3) behavior.

SENSORY-NEURAL ANOMALIES

Auditory and Neural-Crest Anomalies

Historically, since Darwin's observation of deafness in blue-eyed white cats [27], a complex picture has emerged of the embryonic association of the development of neural tissue and melanin pigmentation. The embryonic neural crest is the exclusive source of elements of the sympathetic nervous system including the adrenal medulla, of ganglion cells of the auditory nerve, of Schwann cells, and of melanoblasts. Melanoblasts are the embryonic precursors of melanin-producing melanocytes. There are many instances of the association of a congenital abnormality in the inner ear and abnormal body pigmentation. There is also the abnormality of sympathetic ganglia that innervate the colon (Auerbach's plexus) that produces megacolon in white-spotted mammals. The common cause of these anomalies is a developmental fault in cells of the embryonic neural crest [30, 33, 61, 86, 87, 124, 126].

Studies of the cochlea of deaf white cats have shown both failure of neurons to migrate to the inner ear and demyelination of some that do migrate [5, 6, 101]. Similar conditions are described in humans. The Waardenburg syndrome, Woolf's syndrome, and Ziprkowski-Margolis syndrome all include congenital deafness and white spotting of the skin [82, 96, 120, 132, 133]. The Waardenberg syndrome also includes a white forelock of hair, one blue eye, and sometimes features spiral ganglion agenesis and midline congenital anomalies [70].

During the 1950s and 1960s, research firmly established that inner ear defects and the absence of myenteric ganglia in the large intestine in association with white coat color are due to effects of single genes [5, 8, 12]. Some of the mutant genes causing dominant white or white spotting also appear to have pleiotropic effects on the vestibular portion of the ear, blood, gonads, and on structures not derived from neural crest cells suggesting anomalies at different levels [111]. Research on albino (*cc*) mutations and congenic strains has revealed that the albino gene is associated with susceptibility to audiogenic seizures, reduced auditory functioning, lower body mass, and delay of auditory development [57]. There are probably differences in brain stem auditory pathways between albino and pigmented mammals [57,85]. The degree of hypopigmentation need not be complete. Dilution genes are also associated with a number of sensory-neural anomalies [111].

Visual Anomalies

Anatomical comparison of albino and pigmented mammals has revealed differences between their visual systems. Studies have demonstrated that the visual systems of albino mammals, including humans are anomalous. Anomalies reported in albino mammals include: (1) reduced numbers of uncrossed optic projections to the dorsal and ventral portions of the lateral geniculate nuclei, of anterior and posterior pretectal nuclei, and of superior colliculus; (2) disorganization of patterning (lamination) of optic terminations in dorsal and ventral lateral geniculate nuclei; (3) disorganization of projections from dorsal lateral geniculate nucleus to visual cortex. Abnormalities have been verified in nine species of mammals: cat, rat, ferret, tiger, mouse, mink, guinea pig, rabbit, and humans [17–23, 40, 41, 45–51, 60, 62, 79, 109]. *All* of the albino mammals examined have shown one or more of these anomalies.

The association of albinism and visual anomalies is extensive within albinos. There are implications that there are differences in cortical anatomy [131]. The spectral sensitivity of the eye of albino animals and albino humans is significantly shifted towards the red compared to those of mammals with ocular pigmentation [31]. There is an extensive body of research demonstrating the damaging effects of prolonged periods of exposure to light on the retina of albino rats [1, 9, 69, 105, 106]. Physiological differences between the electroretinograms of albino and pigmented rats or rabbits, apart from those due to intensity, have been documented [97,104].

Differences in optokinetic nystagmus between albino and pigmented animals have been reported. Hahnenberger [52] pointed out that results of studies of optokinetic nystagmus are conflicting because differences between albino and pigmented rabbits were not considered by some researchers. Collewijn *et al.* [15] reported that albino rabbits have inverted optokinetic nystagmus as compared with pigmented rabbits. We have speculated that reduced functional terminations of uncrossed optic fibers in the midbrain may contribute to nystagmus in albinos [26]. Collewijn *et al.* stated that optokinetic inversion could be one cause of spontaneous nystagmus in albinos and pointed out the "perils of using albinos" for visual experiments [15].

Thus, there is an ontogenic parallel in the development of several systems: embryonic migration from the neural crest of pigment cells and peripheral nervous system including the adrenal medulla, Schwann cells, and formation of the auditory, vestibular, and optic systems. Mammals that have complete albinism, white spotting, or generalized hypopigmentation have a high probability of sensory-neural defects.

Sensory Physiology

Melanin pigment is metabolically very active, playing a

key role in sensory physiological processes. Wald [123] postulated analogous functions of the sheath of Schwann cells which surround myelinated neurons, and melanin pigment in the epithelium of the retina. The complete role of melanin in the chemical visual cycle is not known. Experimental evidence indicates that functions of the pigmented retinal epithelium include the uptake of retinol from the extravascular space and its transfer to and from photoreceptor cells [63]. Melanin attracts and binds intermediaries during the visual cycle. Evidence also indicates that melanin acts as an amorphous semiconductor threshold switch [89]. The presence of melanin where charge transfer occurs suggests its ability to function as an electrophysiological material. This may be a contributing factor in the finding that albino rats and mice have longer latencies to peaks of early components of the photically evoked potential than do pigmented rats and mice [20,59]. An additional clue to melanin pigment's metabolic and physiological properties may lie in the suggestion that, as part of a protective function, melanin acts as an absorbent for photoactively-produced free electrons [76,84].

BIOCHEMICAL-METABOLIC ANOMALIES

The identification of anomalies associated with hypopigmentation is partly a matter of ease of detection. The abnormalities most commonly reported involve reproductive, sensory, and neural systems. There is a relative dearth of evidence for metabolic, endocrine, or other biochemical anomalies since these effects are often not readily observable. The following studies of brain, liver, and kidney indicate that albinism is probably associated with alterations of their biochemistry.

Kidney and Liver Metabolism

Albino mice have a greater turnover of tyrosine in the liver than normally pigmented animals [91]. Deletion studies by Gluecksohn-Waelsch and colleagues have shown that genes at or near the albino locus in mice regulate several perinatally-developing enzymes and plasma proteins of liver and kidney cells [38, 42, 43]. Differences in liver cytochrome P-450 levels were found among several strains of albino when compared with pigmented strains of rats [24]. The cytochrome P-450 system involved in oxidative detoxification was reported not to be detectable in newborn albino mice [117]. Genes causing hypopigmentation without complete albinism or white spotting are associated with other biochemical anomalies. For example, the buff (*bf*) gene that produces a dilution of pigment in the mouse affects kidney lysomal glycosidases [53]. Genetic loci around *c* locus including shaker to ruby are the same loci that control liver and kidney enzymes [42].

There is increasing evidence that significant differences exist between albino and pigmented strains of rats in the sensitivity to and metabolism of drugs. For example, the response of the liver to barbiturates has been associated with degree of pigmentation [4, 16, 37, 64]. Albino mice have longer sleep times than pigmented mice treated with either alcohol or pentobarbital [68, 103, 125]. Albino strains of rats require lower doses of pentobarbital for lethal effects than strains of pigmented rats [113]. Albino rats show a linear attenuation of components of the visually evoked potential following progressively increasing dose levels of pentobarbital, as compared with pigmented rats, who show a "rebounding" of the visually evoked potential [25]. A comparison of the effects of pentobarbital on the visually evoked potential in congenic albino and pigmented mice demonstrated a linear effect in the albino and a curvilinear effect in pigmented mice [58]. Metrazol (pentylenetetrazol) lowered the threshold for photically-evoked seizure activity in all hypopigmented strains of rats studied but was found to be ineffective in black rats [36,112].

Evaluation of Drugs

Perhaps the most relevant area of research concerning us is the inappropriate use of albino models to test the effects of drugs for human consumption. Historically the first-level analysis of a drug has been performed on albino animals. For some chemicals hypopigmentation may have no effect, but reports indicate that for a variety of drugs it does make a difference.

The following studies indicate that presence of melanin pigment is necessary to evaluate some effects of drugs, yet new drugs are not generally tested for interaction with melanin. A number of drugs and chemical substances, mainly those that are polycyclic, bind to melanin pigment and are retained for long periods with adverse effects [28, 29, 73, 74]. Albino animals were studied in early autoradiographic investigations using drugs labeled with radioactive isotopes. Research with albino animals indicated that most organs were usually clear of a drug within a few days after a single dose. When Lindquist and colleagues tested pigmented animals melanin was found to accumulate some drugs and keep them bound for months and even years [73,74].

The dangers of not recognizing interactions with melanin are not hypothetical. Clinical observations have been made of the interaction of drugs and melanin pigment. In the latter 1950s and 1960s the use of phenothiazine tranquilizers, especially chlorpromazine, was noted to be associated with pigment disturbances in the eye. Pigment deposits on the iris, cornea, and lens were observed in a high percentage of patients receiving high-dose long-term chlorpromazine therapy. Some patients had chlorpromazine-induced general melanosis with pigment deposited throughout the reticuloendothelial system in the kidney, myocardium, and brain [73].

Chloroquine is a more potent chorioretinotoxic drug than the phenothiazines. Dose levels used for treatment of malaria are considered safe, but higher dose levels used over longer periods in the treatment of collagen diseases can cause retinal and auditory damage because of affinity for melanin-containing tissues [3,55].

The conspicuous feature of labelled chlorpromazine and chloroquine is their selective retention by melanin-containing tissue. In experimental animals high levels of chloroquine in melanin-containing tissues were found 90 days after injection and the amount in pigment of the eye was high one year later [73]. Labelled chloroquine was also found to pass rapidly through the placenta, and to accumulate, and remain in embryonic melanin structures for 90 days [29]. Conversely, chloroquine activity was low in the albino eye within 24 hours after injection and no accumulation was found in any tissue of the albino after 10 days.

Pilocarpine has been used for treatment of glaucoma. The first study in which direct assays of radioactive pilocarpine were used revealed low levels of ocular absorption in the iris of albino rabbits [54]. Later studies found much higher uptake in the iris of pigmented rabbits. The disparity between reports was the result of differences be-

tween albino and pigmented animals. Pigmented irides concentrate pilocarpine. The magnitude of the difference was 10-fold between iris levels in pigmented as compared with albino rabbits [72,80].

Other drugs have known affinity for melanin pigment, including clindamycin, gentamicin, streptomycin, dopamine, epinephrine, norepinephrine, serotonin, and nicotine [2]. Melanin affinity for substances is known to contribute to lesions in the brain, eye, inner ear, reticuloendothelial system, and skin [7, 73, 114]. Administration of melanin-binding drugs during pregnancy may initiate fetal injury; for example, retinal lesions were reported in children whose mothers were treated with chloroquine during pregnancy [55]. In contrast, albino laboratory animals showed no accumulation or retention of tested chemicals.

Most drugs are also tested on animals other than albinos and some are ultimately tested in controlled studies of human subjects. However, in the efforts to determine whether drugs are harmful, some decisions are being based upon first-level analyses in a model system, i.e., in albino animals. As the preceding studies illustrate, some deleterious effects that would occur in a pigmented model would be missed in an albino model. New drugs should be tested on normally pigmented animals so that potentially adverse interactions with melanin pigment or normal levels of chemical precursors of melanin can be ascertained.

For the Food and Drug Administration (FDA), the ramifications of inappropriate animal models being used in drug research are obvious. This is particularly pertinent in view of the FDA's preference to distinguish substances with possible deleterious, e.g., carcinogenic, effects based only upon data from laboratory animals. Results from studies with albino models should not be generalized to pigmented organisms, especially not directly to humans.

Related Metabolic Pathways

The metabolic pathways of tyrosine and of related chemicals are integrally involved in both normal formation of pigment and normal functioning of the nervous system. The brain catecholamines, such as dopamine, epinephrine, norepinephrine, and serotonin are derived from tyrosine and are distributed similarly to neuronal melanin, indicative of the ontogenic and biochemical relationship between neuronal melanin and catecholamines [83,126]. The similarity between the metabolic pathways producing melanin pigment and that producing catecholamines is remarkable. Undifferentiated neural crest cells are labile with their development responsive to environment cues which may produce distinct cellular phenotypes [94,95]. In addition to the neural crest as the origin of both tissue types, the pathways of melanin pigment and of catecholamines are initiated by the conversion of tyrosine to dopa in the presence of enzymes [126]. The similarity of the metabolic pathways of melanin pigment and catecholamines prompted Weston to postulate that neural-crest cell differentiation may be due to differences between the enzymes in each pathway [126]. Their pathways are so similar that the formation of catecholamines provides the pathway for formation of neuronal melanin pigment (Fig. 1).

Abnormally light coloration of the skin and hair can be symptomatic of underlying metabolic disorder because some insufficiencies in amino acid metabolism are reflected in concomitant insufficiencies of active precursors of melanin pigment. Over 50 years ago [56] it was observed that brown-grey coats of rats lighten in color when they are fed a protein deficient diet.

There are a number of genetic disorders that involve both a form of albinism or partial albinism and deleterious effects in other organs or systems. The Chediak-Higashi syndrome [100,130] and another syndrome described by Griscelli *et al.* [44] are both associated with partial albinism and immunodeficiency. These conditions are characterized by frequent pyogenic infections and neutropenia. Cyclic neutropenia is found in hypopigmented dogs [77,78] but is probably not related to the Chediak-Higashi syndrome. There are a number of inherited disorders which involve anomalies of blood cells associated with hypopigmentation [90]. There is a subtle balance between plasma, liver, and cerebral amino acids. Most biochemical disorders that involve immediate precursors of melanin pigment have concomitant changes in skin and hair pigmentation. A higher proportion of hypopigmented mammals have these metabolic disorders simply because of the high correlation between melanin pigmentation and amino acid metabolism. In hepatic encephalopathy [34,35] the interaction of melanin precursors phenylalanine and tyrosine in liver, plasma and brain is readily apparent. In addition to the numerous correlates between hypopigmentation and these types of disorders there may very well be subtle biochemical changes which do not lead to overt disease but which may influence experimental studies using hypopigmented animal models.

There are several human neurological syndromes in which hypopigmentation is a sign of disorder. Phenylketonuria is a congenital deficiency in which there is a block in the oxidation of phenylalanine to tyrosine, and inadequate formation of melanin pigment; the deficiency is associated with severe mental retardation. It has been suggested by Winder [129] that when there is restricted availability of amino acids, cerebral protein synthesis can be affected, and this may be the basis for mental retardation in phenylketonuria and homocystinuria [93,127]. Kwashiorkor, characterized by abnormal amino acid ratios and retardation of growth and motor development, would fall under the same category [119]. Rogawski *et al.* [108] postulated that an as yet unidentified metabolic defect in albinism may be responsible for retardation and psychiatric disorders in several forms of human albinism.

There are other metabolic disorders in which pigmentary changes are symptomatic of underlying disease [93, 127, 130]. These include hyper- and hypothyroid conditions where there are concomitant changes in pigmentation that include hypopigmentation and vitiligo [14,92]. Ontogenic and biochemical parallels between cells of the endocrine glands, carotid body, intestine, stomach, and lung of probable neural crest origin have been pointed out by Pearse in his delineation of the APUD (*a*mine and amine-*p*recursor *u*ptake and *d*ecarboxylation) cell system [98,99]. Bolande incorporated the APUD system into his description of "the neurocristopathies," a number of syndromes related to neural crest development that concomitantly affect pigmentation, including for example von Recklinghausen's disease [11]. I suggest that, for many diseases associated with pigmentary changes, there are unrecognized links between pigment-related amino acid metabolism and both metabolic and morphologic disorders.

BEHAVIORAL ANOMALIES

Until recently, investigators used available strains of rats or mice for behavioral experiments irrespective of genetic background. Many still do. Differences among experiments were attributed to such things as experimental apparatus,

technique, or sampling error. Unreconciled differences were often due to differences among strains of animals. Strain differences in metabolism, learning, and behavior are now expected.

Investigators have compared strains of animals in visual learning tasks using the same background illumination (high) for both albino and pigmented strains. Application of genetic principles to the study of effects of single genes has inspired behavioral testing that revealed absence of effects of albinism in visual learning with training given under dim red light [121,128]. In a summary of 41 behaviors tested in albino and pigmented mice, albinos differed significantly in 20 behaviors [118]. Most behavioral differences between albino and pigmented strains are probably due to suppression of activity or visual learning due to high illumination in the testing situation. Effects of albino genes and strain differences in visual learning paradigms are confounded by effects of illumination, possible retinal damage in the adult albino, and the anatomical anomalies of the commissures and visual systems of albino mammals [9, 20, 22, 71, 122].

For example, over the past 50 years psychologists have used the rat to test whether its relatively small uncrossed optic tract [20,22] is sufficient for learning a discrimination between visual patterns. Investigators testing the functional capabilities of the rat's uncrossed optic tract reported different results. In 1965 Sheridan [115] reported that uncrossed optic fibers are functionally incompetent in albino rats, but not pigmented rats. It was observed in retrospect that experiments differed with respect to the type of rat used. In each experiment the pigmented rats learned to discriminate, while the albino rat was found not to learn (see Creel *et al.*, [26] for review). Subsequently, the finding of a reduced uncrossed optic system in albino rats was reconfirmed in anatomic [22,79] and in electrophysiologic studies [20].

Differences between albino and pigmented models used in research on the effects of microwave irradiation have been reported. A study using albino rats indicated that sodium salicylate, an analogue of aspirin, is a true hypothermal agent, not merely an antipyretic compound [110]. Several species were subsequently tested after microwave hyperthermia or control treatments for generality of effects of sodium salicylate. The hypothermic effects were found to be peculiar to rats, especially albinos, and did not generalize to the guinea pig or rabbit [102]. In another experiment, behavior of albino mice differed from that of pigmented mice when they were exposed to low-frequency magnetic fields [116]. Caution should be exercised in using albino models in microwave research, including studies of induced febrility, unless differences between albino and pigmented animals are resolved.

IMPLICATIONS

Melanin and the metabolic roles of its chemical precursors affect a number of biochemical, developmental, physiological and sensory-neural systems. The investigator using albino animals is using a neurologically and metabolically anomalous model. Where research is based only upon data from albinos, future work, should be paralleled using pigmented models.

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