The Physiology of the Pigmentary System

1 Historical and Comparative Perspectives of the Pigmentary System

1 A History of the Science of Pigmentation

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Introduction

In Europe, prior to the seventeenth century, notions about the origin of human skin color were based largely on myths and fanciful stories passed down from the ancient world. The stories focused on providing explanations for the blackness of Africans. Europeans with an ethnocentric perspective thought that it was necessary to justify the darkness of outsiders rather than to explain their own paleness. In Europe, two theories about the origin of Africans' color predominated. The first proposed that the black hue of African skin was a consequence of the intense sunlight and heat to which Africans were exposed. The second idea proposed that African color was a result of divine intervention, a concept that stemmed from the well-known passage in Genesis describing Noah's curse on Ham and his progeny.

Such traditional views of skin color were questioned during the Age of Discovery. Explorers were returning home from remote regions of the globe and bringing with them descriptions of black-, yellow-, or red-hued peoples. The array of colors fascinated scientists and excited them to investigate how these skin colors originated.

During the sixteenth century, the scientific community prepared for this task. Scientists learned new techniques of human dissection and new methods of chemical analysis. More importantly, they adopted a new philosophical approach for the study of natural phenomena. Rather than analysis of phenomenon based on a priori assumptions, they based their analyses on firsthand observations and experimentation. By the seventeenth century, anatomists and physicians had begun to collect objective data about skin color. For the next two centuries, so many important observations had been collected about the seat of skin color and the causes of its diversity that, as one researcher boasted, "a good sized volume was scarcely large enough to contain them."

The furious pace of forward progress was slowed somewhat in the early part of the nineteenth century when skin color scientists in both Europe and America were drawn into acrimonious debates over social issues, especially slavery and the place of "peoples of color" in the family of man. By the end of the century, the slavery issue had been settled, and the discovery of the cell and improved methods for the microscopic examination of the skin had stimulated the discipline to set off in new directions.

In retrospect, it is clear that the science of skin color had completed its early phase of development by the 1840s. With the discovery of the cellular nature of the epidermis, the "modern" phase of skin color science had begun (Meirowsky, 1940). This chapter briefly summarizes the first 250 years of the earlier phases of pigment research, from its birth in the 1600s to its "coming of age" in the 1840s. A history of the modern era, from the 1840s to the present, may be found in reviews by Becker (1959) and Nordlund *et al.* (1989).

Early Anatomic Discoveries

To the ancient Greeks and Romans who were acquainted with the peoples of Ethiopia, the black color of the Africans was regarded as their most characteristic and most curious feature. Greek and Roman scientists were not equipped to investigate the causes of dark complexions in a meaningful way. They understood little about dissection of individual tissues and were unable to sort out the anatomic details related to the skin. They regarded the skin as an amorphous membrane made from the congealing of "moist exhalations" driven to the surface of the body by internal heat. They believed that the color of skin was imposed either from outside by the sun or by some inner humor. These notions about skin color persisted through the Middle Ages and into the Renaissance. In 1543, Vesalius succeeded in splitting the skin into two layers by applying a burning candle to the abdomen of a living subject. He did not examine the skin layers for their content of color. It was not until 75 years later that the first "scientific" study of skin color was performed.

In 1618, Jean Riolan the younger, a Parisian anatomist, was the first person to make a detailed analysis of skin color. He used a technique similar to that of Vesalius to separate the skin of a black subject into two layers. But he used a vesicant rather than a flame to produce a blister and carefully examined the two layers for their color and texture. He found that, while the top of the blister (the cuticle) was pigmented, the base (the cutis) remained white. "Color . . ." he announced ". . . lay in the outer layer, and did not go so deep as the true skin" (Riolan, 1618).

To Riolan, this finding reinforced the idea that heat and sunlight were the ultimate causes of blackness. Riolan reasoned that, if the sun caused skin darkening, it was expected that the outer cuticle would be darker than the inner cutis.

A few years later, Alexander Read, an anatomist working in London, repeated Riolan's experiments and found the same results. However, Read offered a different interpretation. The skin pigment, he concluded, was not caused by singeing the body's surface. He concluded rather that skin color was derived from the body's inner humors. As they escaped through the skin, some of the elements became attached to the surface and dried, thus producing the pigment. Negroes, he argued, had darker skin because they had larger pores than whites, a morphologic variation allowing greater volumes of their humors to escape leaving behind larger amounts of black "remnants" of the humors (Read, 1642).

Perhaps the most detailed analysis of skin color in the seventeenth century was carried out by the distinguished writer and physician, Sir Thomas Browne. Browne had listened carefully to the accounts of explorers who had found variously colored races, and he concluded from these accounts that color did not arise from the influence of climate. "If the fervor of the Sun were the cause of the Negroes' complexion, . . ." he wrote, ". . . it is reasonable to assume that inhabitants of the same latitude, subjected unto the same vicinity of the Sun, partake of the same hue and complexion, which they do not." In addition, he noted that Africans who had been transplanted into ". . . cold and phlegmatic habitations . . ." had not turned white, but ". . . continued their hue, both in themselves and their generations." He rejected the idea that skin blackness was acquired from a ". . . power of imagination . . ." or from ". . . anointing with bacon and fat substances." Instead, he thought that the tincture of the skin was based on an inborn trait, a trait that was passed from father to son by the sperm.

Browne was not an armchair scientist. His diary records the outline of numerous experiments he carried out to determine for himself the seat of color. For example, he set out to make a ". . . blistering plaster in a negroes skinne and trie if the next skin will bee white . . ." and to see whether a ". . . vesication will do anything upon a dead cold body." He even urged his son Edward, a medical student, to carry out additional studies. He wrote to him asking that he ". . . separate the skin of a black person with boiling water and take notice of the cuticula and cutis and observe how the scarres become whiter or less blacke than any other parts." He also urged him to ". . . touche the skin with aqua fortis and see how it will alter the colour." Unfortunately, Browne did not record the results of these experiments (Keynes, 1964).

Another seventeenth century polymath, Robert Boyle, devoted a chapter of his book *Experiments and Considerations Touching Colours* to what he called "the Cause of the Blackness of those many nations which by one common Name we are wont to call *Negroes*." He examined the various causes proposed at that time and denied that either Noah's curse on Ham or "heat alone" could produce a true blackness. Instead, he focused on principles of inheritance, concluding that the "Principal Cause of the Blackness of *Negroes* is some Peculiar and Seminal Impression." As evidence, he reported that "the off-spring of Negroes, transplanted out of Africa, retain still the complexion of their Progenitors" (Boyle, 1664).

Malpighi's Innovation: the Rete Mucosum

Riolan's contention that the cuticle was the seat of color had been in place for less than a century when it was superseded by an entirely different notion proposed by the Italian anatomist, Marcello Malpighi. In 1667, Malpighi stated that the seat of color was not the cuticle. Rather, he proclaimed that color was located in a separate layer of the skin sandwiched between the cuticle and the cutis. He named this layer the rete mucosum. The discovery of rete came about in the following way. In 1665, Malpighi had been searching for the structures that mediated the sensation of taste, and he succeeded in finding large papillae just below the surface of the tongue. Turning to the skin to see if he could find similar structures that mediated touch, he found that he was unable to separate the skin's layers properly by boiling, the method that he had used previously. He was forced to use putrefaction, an old dissection technique in which the separation of parts is enhanced by allowing a small piece of tissue to decompose partially. Using this method, he prepared skin from cadavers and found that he could easily lift the cuticle from the cutis. By this method, he was able to identify the dermal papillae. However, he also found a mucoid material draped over the papillae, which he regarded as a protective covering. The material had a netlike appearance when seen from above, so he called it the rete mucosum. Malpighi's experiments were not directed at discovering the proximate cause of skin color. However, in one experiment in which he used skin from an Ethiopian cadaver, he noted that the mucoid material was tinged black. On the basis of this finding, he later wrote "It is certain that the cutis (of the Ethiopian) is white, as is the cuticula too; hence all their blackness arises from the underlying mucous and netlike body" (Malpighi, 1665).

Malpighi did not follow up on his discovery of the "seat of color" but the putrefaction technique he used allowed the layers of the skin to be separated gently. The method produced reliable results, and other investigators soon expanded on Malpighi's finding. In 1677, three years after Malpighi published his findings, Johann Pechlin, a Dutch anatomist, used Malpighi's method of dissection to make a thorough study of Ethiopian skin. In one experiment, after he lifted off the cuticle, he scraped away the black mucous and reapplied the scarf to the cutis. He reported that ". . . a whiteness came forth immediately of the sort seen often enough in Europe. In truth the surface of the skin was scarcely unattractive." Pechlin was concerned that his results obtained using cadaver skin might not be the same had he studied living skin. To his dismay, he was unable to convince living subjects to cooperate in his experiments ". . . because of I don't know what sort of evil on the part of the Negroes" (Pechlin, 1677).

A few years later, the Dutch microscopist Antoni van Leeuwenhoek, in a letter to the Royal Society of London, reported on his observations made using his microscope of the skin of a black Moorish girl. "I took from several parts of the arms the outer skin with a fine little instrument and found that it consisted of little scales. Putting these scales before my microscope I found them to be not as transparent as those of my skin." Van Leeuwenhoek concluded that the black color of the skin was the result of the black scales, and that "the little vessels which form the scales of the Moors" may possibly develop a slightly darker color (*Collected Letters of Antoni van Leeuwenhoek, 1683–1684*; see Schierbeek, 1952).

If one follows Malpighi's directions for uncovering the rete, as the cuticle is lifted off one observes tiny mucoid threads bridging the angle between the two layers. William Hunter described them as ". . . an infinite number of filaments, as fine as the most delicate threads of a spider's web, that pass between the cutis and the more external integuments" (Hunter, 1764). According to some anatomists, the threads were tiny vessels. This idea led some of the more inventive investigators to propose that the coloring matter in Africans' skin was not the mucous material itself but was a black fluid contained within the web of small vessels. One contemporary observer wrote ". . . between the outward and inner skin of the corpse can be found a kind of vascular plexus, spread over the whole body like a web or net, which was fill'd with a Juice as black as Ink" (Marana, 1801).

It became something of a challenge to prove unequivocally that these filaments were in fact "vessels." In anatomic laboratories, the identification of small vessels in anatomic preparations relied on their visualization after they had been injected with colored glue or isinglass. Only a few investigators were skilled enough to inject these ". . . most delicate threads." One anatomist who was given credit for the first demonstration of this vascular network was William Baynham, an American who had moved to London in 1769. Although Baynham never published his findings, he placed his specimens on exhibition in John Hunter's anatomic museum. Not all Baynham's colleagues were convinced by his discovery. William Cruickshank made a careful study of Baynham's preparations and later wrote that he was ". . . not perfectly satisfied" with them. He concluded that Baynham had not injected the vessels of the rete, but rather a series of vessels that lay between the rete and the cutis (Cruickshank, 1795).

In the eighteenth century, the attention of researchers began to move from the anatomy of the rete to the "nature" of the coloring matter itself. Early attempts to collect and analyze material from the rete were not productive. Alexis Littre, a French surgeon, soaked pieces of skin from a Negro cadaver for a week either in warm water or in spirits of wine but was unable to extract any of the coloring matter (Littre, 1720).

A few years later, another French scientist, Pierre Barrere, in an essay submitted to the Academy of Bordeaux in 1741, denied Malpighi's claim that the pigment of Africans' skin arose from the "*corps reticulaire*." It is evident, he wrote, the coloring matter in the skin of Africans was bile. He reported that he had examined cadavers of Africans and observed that "the bile is black, and the blackness of the skin is in proportion to the blackness of the bile."

Later in the century, another investigator attempted to prove that the pigment of Africans was derived from bile. Samuel Stanhope Smith, a professor of moral theology at the College of New Jersey, had learned from an American colleague that bile exposed to the sun and air changed its color to black. Smith hypothesized that, in southern climates, the secretion of bile was augmented and, when the bile reached the skin, it became ". . . more languid and almost fixed." In the skin, the aqueous parts of the bile easily escape through the pores of the skin by perspiration, while the more dense portion remained in a glutinous state within the rete. There, it received the repeated radiation from the sun and atmosphere and turned black. Smith believed that a cold environment would reverse the process of darkening and render the complexion ". . . clear and florid." According to Smith, if Africans moved to temperate climates from Africa ". . . they would soon lose their imposed color and become the color of Europeans" (Smith, 1788).

Johann Friedrich Blumenbach, the German ethnologist, also proposed that bile was the coloring agent of the skin. He had learned that bile was made of a mixture of carbon and hydrogen. He suggested that, as the bile reached the skin, the hydrogen it contained became more volatile than the carbon and combined with atmospheric oxygen. This reaction left behind a black carbon residue that became embedded in the Malpighian mucous and caused the skin to darken (Blumenbach, 1865).

Another "chemical" theory was advanced by the young Humphrey Davy in 1799. Davy thought that light had a great affinity for oxygen and could extract it from other compounds. Davy had evidence that the mucous material of the rete was made of a colorless mixture of carbon, nitrogen, and oxygen. He proposed that sunlight extracted the oxygen from this mixture and left behind a black material made of carbon and nitrogen. To Davy, this explained differences in skin hues found throughout the world. "In northern latitudes, where the inhabitants are less exposed to light, the rete continues to contain its full proportion of oxygen, and the inhabitants are lighter in color. In the torrid zone, on the other hand, where the sun was especially intense, larger quantities of oxygen would be removed, and the blackness peculiar to the negroes will be found." Davy had no direct proof that light could subtract oxygen from the skin, but he did cite other chemical experiments to support his claim. He reported that, when a compound that binds oxygen, such as sulfur of potash, is applied to the skin of a white person, the skin blackens. When a compound that gives off oxygen, such as muriatic acid, is applied to the skin of a Negro, it lightens (Davy, 1799).

An even more imaginative notion about the nature of skin color was suggested by Immanuel Kant. Kant based his theory on the well-known capacity of phlogiston to turn blood a black color. Phlogiston was an imaginary element considered to be the essential principle of combustion. It was said to be

released from the body through the lungs as part of the metabolic process. Kant believed that, in regions of the globe where the atmosphere was heavily phlogisticated, such as the coast of Africa, it would be impossible to eliminate all the body's phlogiston by breathing. Kant proposed that the excess phlogiston would travel through the circulation and, on reaching the skin, it would precipitate in the ends of the small cutaneous vessels and turn the skin black (Lovejoy, 1959).

Claude Le Cat, a French physician, claimed that the source of Africans' blackness was neither bile nor blood. He said that the black mucous, which he called ethiops, was found only in Africans and that it was secreted directly into the skin through the tips of the cutaneous nerves (Le Cat, 1765).

Although most early scientists believed that skin pigment was derived from some "internal" source such as bile or blood, a few investigators decided that the coloring matter was produced by glands within the skin itself. The earliest version of this hypothesis was offered by an English anatomist, Edward Tyson. He proposed that the black colour in Negroes' skins came from glands that were full of a "black liquor." He suggested that the climate might alter the glands so that ". . . they might separate from the mass of blood a differing humor from White, and by this means give a different hue to the inhabitants" (Montagu, 1943).

Two French researchers, G. H. Breschet and Roussel de Vauzeme, reported that they had found a ". . . chromatogenous apparatus . . ." in the cutis which secreted the black mucous. They said that the mucous was deposited on the surface of the dermal papillae through short, excretory ducts emanating from glandular parenchyma located in the cutis (Plumbe, 1837).

Another French investigator, M. Gaultier, also argued that the coloring matter was secreted within the skin but not from glands. The pigment of the skin, he said, was produced instead from hair bulbs. Gaultier's claim was based on the results of an experiment he carried out on a living subject. He burned the skin of a Negro and then closely observed the pattern of repigmentation during the healing process. According to Gaultier, the pigment appeared first around the "pores" through which the hairs exited and only later did it radiate out to cover the entire area of the burn (Prichard, 1813).

Differences Between Blacks and Whites

As a more complete picture of skin color began to emerge by the end of the eighteenth century, political and social forces required the disciplines of anatomy and biology to take on a social dimension. Advocates of black slavery argued that Africans were not the "brothers" of Europeans but rather were the product of a separate creation. Skin color, the most obvious marker of racial identity, was forced to the center of the debate over the unity of mankind. The polygenists began looking for "significant" anatomic differences between blacks and whites to prove they were separate species. Monogenists began looking for evidence of similarities.

Bolstering the polygenist cause was the English anatomist, John Gordon. Gordon claimed that whites, unlike blacks, had no rete mucosum. "I have satisfied myself by many dissection that in the Negro there is a Black membrane interposed between the epidermis and true skin upon which their dark color entirely depends . . . But after the strictest examination I have not been able to find any light colored rete mucosum in the inhabitants of Great Britain, nor in those of other nations resembling them in color" (Gordon, 1815).

Several anatomists disagreed. Richard Harlan, a young lecturer in anatomy from Philadelphia, wrote that ". . . the existence of the rete mucosum in the white race, so frequently denied, has been demonstrated occasionally in the European by skilful anatomists and if not deceived I myself have discovered it several times in a living European subject, by raising the epidermis with a blister, especially upon the back of the hands and the neck" (Harlan, 1835).

Charles Caldwell, who had moved from Philadelphia to become a professor in a medical college in Lexington, Kentucky, reported that he too found the rete in both races, although the structures were not identical in appearance. "The rete mucosum in blacks is comparatively thick, while in the Caucasian, the rete is present but it is much thinner." In spite of this similarity, however, Caldwell concluded that Negroes and Caucasians were sufficiently distinct to be called separate biological species (Caldwell, 1830).

Experiments of Nature

In addition to the work carried out by anatomists and chemists in dissecting rooms and laboratories, many physicians made important contributions to the fund of information about skin color through reporting and analyzing patients with clinical problems. John Josselyn, a physician from England who was visiting the Massachusetts Bay Colony in 1675, was one of the first physicians to advance the science of skin color by using observations based on a clinical case. While in Boston, Josselyn had been called upon to lance a "corruption" in the palm of a "Moor." Later, he described his findings. "After I lanced it, I perceived that the Moor had one skin more than Englishmen, deeper in colour than our European veins, and upon it rests the epidermis" (Josselyn, 1675).

Samuel Marcy, a physician from rural New Jersey, reported the case of an albino girl. After providing a full account of her family history, including the fact that she had two albino sisters, he went on to consider the cause of the disorder. "The mother accounts for the appearance of the child by attributing it to a severe fright she receive by the falling down of an old white mare she was driving," wrote Marcy. "Although I was unwilling to admit at first that the Great Creator ever left his work in so loose a manner, that the imagination of the mother should alter or determine form or color of her children, the birth of two other albino children go further to strengthen the doctrine that the mind of the mother may affect the fetus in utero" (Marcy, 1839).

John Morgan, from Philadelphia, reported the case of Adelaide, a pied Negro girl from the West Indies. Like Marcy, Morgan considered the possibility that maternal impression might cause the disorder. Morgan related that, while pregnant, the mother of the girl ". . . delighted in laying out all night in the open air, and contemplating the stars and planets. Whether the strong impression made upon the mother of Adelaide by the nightly view of the stars and planetary system may be the cause of the very extraordinary appearances in this girl, everyone will have to determine for themselves" (Morgan, 1784).

During the seventeenth and eighteenth centuries, the pigment disorder that attracted most attention among the medical community, as well as the general public, was vitiligo vulgaris. In 1697, a remarkable case was presented to the Royal Society by William Byrd, a Virginian who had recently returned to London after a visit home. Under the title "An Account of a Negro-Boy that is dappeld in several Places of his Body with White Spots," Byrd reported that the boy was born in Virginia of black parents, who was "well till 3 years old, and now was speckled of his breast and back and that no fancy had taken his Mother." The spots he wrote are "wonderfully White, at least equal to the skin of the fairest Lady. His Spots grow continually larger and larger, and 'tis probable, if he lives, he may in time become all over white." Thomas Jefferson described an African slave whom he encountered on his own plantation. He described the man as "A Negro man within my knowledge, born black and of black parents, developed when a boy, a white spot on his chin. This continued till he became a man, by which time it had extended over his chin, lips, and the neck on that side. He is robust and healthy and the change of color is not accompanied with any sensible disease, either general or topical" (Jefferson, 1904).

Charles Peale, the painter and natural historian, also described a case under the title "An Account of a person born a Negro who afterwards became white" (Peale, 1791).

The case of vitiligo that attracted most attention during this period from both lay and medical communities was Mr Henry Moss. At the age of 38 years, Moss first noted a change in the color of his skin. The change began on his fingers and hands and extended over his arms, legs, and face. Six years later, in the summer of 1796, Moss traveled from his home in Maryland to exhibit himself for money at the Black Horse Tavern in Philadelphia. He became a popular attraction and, according to one account, was so well known to the local citizens ". . . that his name was almost as familiar as John Adams, Thomas Jefferson, or James Madison" (Caldwell, 1855).

Several prominent physicians from Philadelphia visited Mr Moss. Benjamin Barton, a professor at the medical school, was impressed with the distribution of the white spots. Noting that Moss' color had disappeared completely from his armpits, Barton suggested initially that it was likely that the pigment had been washed away by perspiration. Charles Caldwell also examined Moss and was skeptical of Barton's interpretation. He decided to study Moss in detail. "Anxious to know as much of his case as possible, I took him in some measure under my care, . . . and . . . for a slight reward made on him such experiments as suited my purpose. While thousands visited and gazed at Moss as an object of curiosity and wonder, I alone endeavored to make him a source of scientific information." Caldwell asked Moss ". . . to excite by exercise a copious perspiration to ascertain whether the fluid perspired by the colored portions of the skin was itself colored. And I found that it was not." Caldwell examined Moss' skin and found that the rete mucosum had disappeared from the depigmented areas. He concluded that the rete had been removed ". . . by means of absorption." Moss' sensitivity to low temperatures he thought supported his theory that Moss was losing his rete. He concluded that Moss' true skin was now "protected" from a cold atmosphere by nothing but the cuticle (Caldwell, 1855).

Samuel Stanhope Smith, who had earlier pioneered the idea that African blackness was caused by environmental factors, was another visitor. He was accompanied by two other gentlemen ". . . of whom none are more capable of observing a fact of this nature with a sound and accurate judgment." Smith paid great attention to the pattern of Moss' pigment loss and concluded that this provided elegant proof of his hypothesis. "Although there was evidently a strong and general tendency in the constitution of this negro to a change of color, yet this tendency was much longer resisted in those parts of the body which were most exposed to the immediate action of the sun's rays. As he was a laboring man, wherever there were rents in the thin clothes which covered him there were generally seen the largest spots of black." From this pattern, Smith inferred that ". . . where any dark color has been contracted by the human skin, the solar influence alone, and the free contact of the external air, will be sufficient to continue it a long time even in those climates which are most favorable to the fair complexion" (Smith, 1810).

Benjamin Rush suggested perhaps the most unusual hypothesis to explain Moss' pigment loss. In a paper published in 1799, Rush argued that it was the blackness of Moss, and not his white spots, that represented his disease. I shall prove, he wrote, that ". . . the color and figure of our fellow creatures who are known by the epithet of negroes are derived from a modification of that disease which is known by the name of Leprosy." Rush went on to explain that the black color of the negroes, their thick lips, and their insensitivity to pain were all common signs of leprosy. He suggested that it was likely that leprosy was an infectious disorder ". . . since a white woman in North Carolina living with a black husband has not only acquired a dark color but also several features of a negro." Rush proposed that Moss was not suffering from a disease but was actually undergoing a spontaneous cure of one. "If the color of negroes is a disease . . ." he added, ". . . let science and humanity combine their efforts and endeavor to discover a remedy for it." From his experience with other ailments, Rush suggested that bleeding or purging be tried to lessen the black color (Rush, 1799).

The Beginnings of Modern Pigment Research

The "early" phase of pigment research ended in the 1840s when the cell theory ended the rete's reign as a separate amorphous layer of the skin and assigned the seat of skin color to the lower portion of a cell-rich epidermis. Microscopic anatomists had also discovered that the pigment was not in the form of a liquid or mucoid material but was rather composed of tiny intracellular granules. With the discovery that a population of dendritic cells derived from the neural crest served as the source of the coloring matter for the skin and hair, the "modern" phase of pigment research moved into high gear. For the past 150 years, researchers have relied on a melanocyte-centered paradigm to lead them along new paths of discovery. To see how far their investigations have proceeded and how wide-ranging their interests and disciplines, one needs only to look through the remaining chapters in this volume.

References

Becker, S. W. Historical background of research on pigmentary diseases of the skin. *J. Invest. Dermatol.* 32: 185–196, 1959.

Blumenbach, J. F. *The Anthropological Treatises of Johann Friedrich Blumenbach*. London: Longman Green, 1865.

Boyle, R. *Experiments and Considerations Touching Colours*. London: Henry Herringman, 1664, pp. 151–167.

Caldwell, C. *Thoughts on the Original Unity of the Human Race*. New York: E. Bliss, 1830.

Caldwell, C. *Autobiography of Charles Caldwell, MD*. Philadelphia: Lippincott, Grambo and Co., 1855.

Cruickshank, W. *Experiments on the Insensible Perspiration of the Human Body*. London: George Nicol, 1795.

Davy, H. Essays on heat and light. In: *Contributions to Physical and Medical Knowledge Principally From the West of England*, T. Beddoes (ed.). Bristol: Biggs and Cottle, 1799, pp. 193–198.

Gordon, J. *A System of Human Anatomy*. Edinburgh: William Blackwood, 1815.

Harlan, R. *Medical and Physical Researches*. Philadelphia: Lydia Bailey, 1835.

Hunter, W. Remarks on the cellular membrane and some of its diseases. *Med. Observ. Inquiries* 2: 26–55, 1764.

Jefferson, T. *Notes on Virginia, in the Writings of Thomas Jefferson*. Washington, DC: Thomas Jefferson Memorial Association, 1904.

Josselyn, J. *An Account of Two Voyages to New-England*. London: G. Widdowes, 1675.

Keynes, G. *The Works of Sir Thomas Browne*. Chicago: University of Chicago Press, 1964.

Le Cat, C. N. *Traite de la Couleur de la Peau Humaine en General, de celle des Negres en Particulier, et de la Metamorphose d'une de ces Coleurs en l'autre, soit de Naissance, soit Accidentellement*. Amsterdam, 1765.

Littre, A. *La Peau in Histoire de l'Academie Royale des Sciences*. Paris: Hochereau, 1720, pp. 30–32.

Lovejoy, A. O. *Kant and Evolution in Forerunners of Darwin*. Baltimore: Johns Hopkins, 1959, pp. 173–206.

Malpighi, M. *De Externo Tactus Organo Anatomica Observatio*. Naples: Apud Agidium Longu, 1665.

Marana, G. P. *Letters Written by a Turkish Spy*, vol. 8. London: Vernor and Hood, 1801.

Marcy, S. S. On the albino. *Am. J. Med. Sci.* 24: 517–518, 1839.

Meirowsky, E. A critical review of pigment research in the last hundred years. *Br. J. Dermatol.* 52: 205–217, 1940.

Montagu, M. *F. A. Edward Tyson, MD, FRS, and the Rise of Human and Comparative Anatomy in England*. Philadelphia: The American Philosophical Society, 1943, pp. 212–213.

Morgan, J. Some account of a motley coloured, or pye, negro girl and mulatto boy. *Trans. Am. Phil. Soc.* 2: 392–395, 1784.

Nordlund, J. J., Z. A. Abdel-Malek, R. E. Boissy, and L. A. Rheins. Pigment cell biology: An historical review. *J. Invest. Dermatol.* 92(Suppl.): 53s–60s, 1989.

Peale, C. W. Account of a person born a negro, or a very dark mullato, who afterwards became white. *Univ. Asylum Columbia Mag.* 2: 409–410, 1791.

Pechlin, J. N. *Du Habitu & Colore Aethiopum Qui Vulgo Nigritae*. Koln: Joach Reumani, 1677.

Plumbe, S. *A Practical Treatise on the Diseases of the Skin*. London: Sherwood, Gilbert & Piper, 1837, pp. 9–16.

Prichard, J. C. *Researches into the Physical History of Man*. London: John and Arthur Arch, 1813, pp. 163–164.

Read, A. *The Manual of the Anatomy or Dissection of the Body of Man*. London: Francis Constable, 1642.

Riolan, J. *Anthropographia*. Paris: Hadrianum Perier, 1618.

Rush, B. Observations intended to favour a supposition that the black color (as it is called) of the negroes is derived from leprosy. *Am. Philos. Soc. Trans.* 4: 289–297, 1799.

Schierbeek, A. (ed.). *Collected Letters of Antoni van Leeuwenhoek, Vol. IV, 1683–1684*, Amsterdam: Swets & Zeitlinger, 1952, pp. 245–251.

Smith, S. S. *An Essay on the Causes of the Variety of Complexion and Figure in the Human Species*. Edinburgh: C. Elliot, 1788.

Smith, S. S. *An Essay on the Causes of the Variety of Complexion and Figure in the Human Species*. New Brunswick: J. Simpson and Co., 1810.