Human Colors—The Rainbow Garden of Pathology

What Gives Normal and Pathologic Tissues Their Color?

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• ***Context.***—**Colors are important to all living organisms because they are crucial for camouflage and protection, metabolism, sexual behavior, and communication. Human organs obviously have color, but the underlying biologic processes that dictate the specific colors of organs and tissues are not completely understood. A literature search on the determinants of color in human organs yielded scant information.**

Objectives.—**To address 2 specific questions: (1) why do human organs have color, and (2) what gives normal and pathologic tissues their distinctive colors?**

Data Sources.—**Endogenous colors are the result of complex biochemical reactions that produce biologic pigments: red-brown cytochromes and porphyrins (blood, liver, spleen, kidneys, striated muscle), brown-black melanins (skin, appendages, brain nuclei), dark-brown lipochromes (aging organs), and colors that result from tissue structure (tendons, aponeurosis, muscles). Yellow-orange carotenes that deposit in lipid-rich tissues are only produced by plants and are acquired from the diet. However, there is lack of information about the cause of color in other organs, such as the gray and white matter, neuroendocrine organs, and white tissues (epithelia, soft tissues). Neoplastic tissues usually retain the color of their nonneoplastic counterpart.**

Conclusions.—**Most available information on the function of pigments comes from studies in plants, microorganisms, cephalopods, and vertebrates, not humans. Biologic pigments have antioxidant and cytoprotective properties and should be considered as potential future therapies for disease and cancer. We discuss the bioproducts that may be responsible for organ coloration and invite pathologists and pathology residents to look at a "routine grossing day" with a different perspective.**

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"I want to know one thing. What is color?"

—Pablo Picasso

Nature delights us with a great variety of colors that result from the reflection of a particular wavelength of light from an object. Colors are important to all biologic organisms (that is, microorganisms, plants, and animals) because they are crucial for camouflage and protection, metabolism, sexual behavior, and communication. In general, coloration of organisms results from the production of molecules derived from cyclic compounds.

The human body and its organs have colors, that is, the liver is brown, the heart is red, bones are white, and so on. Although this is obvious and established, the reason why organs have a particular color is not completely understood. Pathologists, more than any other physicians, should be aware of the importance in recognizing normal and abnormal gross organ features—color being one of them—that translate into specific pathologic processes. Because cells are microscopic and colorless as single units, they result in a given color only when they accumulate in millions. Unhealthy and/or neoplastic tissues usually retain the color of the cells from which they derive but may also exhibit completely different color characteristics. We performed a literature search related to the biochemical source of coloration in human organs, and to our surprise, scant information is available. Because of this information gap, 2 fundamental questions were asked: why do human organs have color, and what gives normal and pathologic tissues their distinctive colors? The answers to these simple questions are elusive, even with the current revolutionary advances in molecular biology and biochemistry.

The biochemical processes related to pigment production in plants and animals could be an enormous resource to explain the color in human organs. Herein, we attempt to give a biochemical explanation for the basis of the color of human organs that, to our knowledge, is not currently available in the medical literature. None of the authors are experts in the field of biochemistry or chromatics, but all are instinctually interested in understanding more about human biology. We discuss in a simple manner the bioproducts and their physiologic importance that may be responsible for tissue coloration. We invite pathologists and pathology

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PRODUCERS OF COLOR IN HEALTHY AND NEOPLASTIC TISSUES

Carotenes and Carotenoids

In 1937, the Nobel Prize in chemistry was awarded to Paul Karrer for the description of the chemical structure of carotenes and vitamin A. Carotenes are unsaturated hydrocarbons chemically derived from isopentenyl pyrophosphate and terpenes, and include α, β, γ, δ, ε, and ζ carotenes, lycopenes, and xanthines.[1] Carotenes are fat-soluble molecules that can produce all the colors of the visible spectrum (purple, blue, green, yellow, orange, and red) and are synthesized only by plants.[2,3] Carrots (*Daucus carota* var. *sativus*), tomatoes (*Solanum lycopersicum*), and beets (*Beta vulgaris*) are examples of vegetables containing large amounts of orange, red, and purple carotenes, respectively (Figure 1, A). The word *carotene* derives from the Latin *carota* (carrot) and *lycopene* derives from the modern Latin *lycopersicum* (tomato). Carotenes also give color to leaves and fruits, but the primary green pigment chlorophyll is dominant (Greek *chlóros* = green). Once a leaf or a fruit ripens or dies, chlorophyll is degraded, and yellow, orange, and/or red carotenes become apparent.[4] This is why leaves change color during fall, and why a banana (*Musa acuminata*) turns yellow when it's ripe. Xanthines (Greek *xanthos* = yellow) are yellow pigments (zeaxanthin, lutein, canthaxanthin) that give color to several organisms (Figure 1, A). Staphyloxanthin is the pigment that gives *Staphylococcus aureus* its golden-yellow color, and the second name *aureus* is Latin for gold (*aurum*). This pigment is a virulence factor that helps the organism escape death by neutrophils.[5]

Animals are unable to produce carotenes and can only obtain them from their diet. Because carotenes are lipophilic, they associate with lipid-rich tissues. The abundance of certain carotenes in the diet of animals is reflected in the colors of their plumage, fur, or skin. For example, the blue-footed booby (*Sula nebouxii*) owes its peculiar blue-colored beak and legs to the high amount of blue carotenes present in fish and shellfish native to the Galapagos coast. Similarly, flamingos (*Phoenicopterus* spp) are born with gray feathers but develop a beautiful pink plumage following the deposit of red carotenes found in the fish and shellfish they eat (Figure 1, B).[6] A similar phenomenon can occur in humans. Physicians are familiar with the terms *carotenemia* (or *xanthoderma*) and *lycopenemia*, the yellow-orange skin discoloration that occurs after excessive consumption of carrots, tomatoes, or beets. Each animal species, including humans, metabolizes certain carotenes but not others. Thus, our tissues would not turn blue (fortunately!) even if we were to consume the blue-footed booby's diet. Humans metabolize yellow and orange carotenes but not blue or red ones for unknown reasons. To understand how carotenes give color to a single cell, one can look at a raw egg. The yellow tinge of the egg "white" and the bright yellow-orange yolk color are due to the accumulation of carotenoids and retinol (also a carotene) (Figure 1, C).[7]

The α-carotene and β-carotene, lycopenes, and xanthines are the most common carotenes in human tissues.[8,9] They are absorbed and deposited in lipid-rich tissues even before we are born (provided from the mother's diet). Hypothetically, the adipose tissue of a human never exposed to carotenes should be white and not bright yellow, but this scenario does not exist because we ingest carotenes every day from our diet. The adrenal glands and testes are the organs with the highest concentration of β-carotene, followed by the liver.[9] However, any organ or tissue with high lipid content will absorb carotenes and exhibit a bright-yellow or orange coloring, such as, the first 2 layers of the adrenal gland cortex (zona glomerulosa and fasciculata, rich in aldosterone and lipids), the ovarian corpus luteum, the macula lutea in the eye (rich in lutein and zeaxanthin), organs rich in fat (pancreas, parotid gland), and adipose tissues.[10] The neoplastic counterparts of these organs and in general, tumors with high lipid content, such as lipomas, fibrolipomas, well-differentiated liposarcomas, lipoleiomyomas, adrenal cortical adenomas, and carcinomas, such as clear cell renal cell carcinomas, steroid cell tumors, fibrothecomas, and schwannomas are invariably yellow or golden yellow (Figure 1, D through J). Xanthomas and orange palpebral spots are examples of subcutaneous lesions also colored by carotenes.[11] Curiously, not all types of lipids are tinged by carotenes. Myelin, the most abundant lipid of the central and peripheral nervous system, remains white despite the amount of carotenes in our body. It is possible that its chemical composition of sphingomyelin, phosphorylcholine, and ceramides somehow prevents carotenes from being deposited, or the minute amounts present are grossly imperceptible.

What are the functions of carotenes in living organisms? In plants, carotenes are crucial for photosynthesis because they transmit light energy to chlorophyll in the chloroplast. They also protect plant tissues from the action of toxic singlet oxygen. In humans, carotenes not only protect cells from the effects of ultraviolet light but also from the toxic effects of reactive oxygen species.[9] Therefore, carotenes are potent antioxidants and quenchers of toxic byproducts derived from metabolic reactions. Vitamin A or retinol (which gives the retina some of its color, hence the name) is

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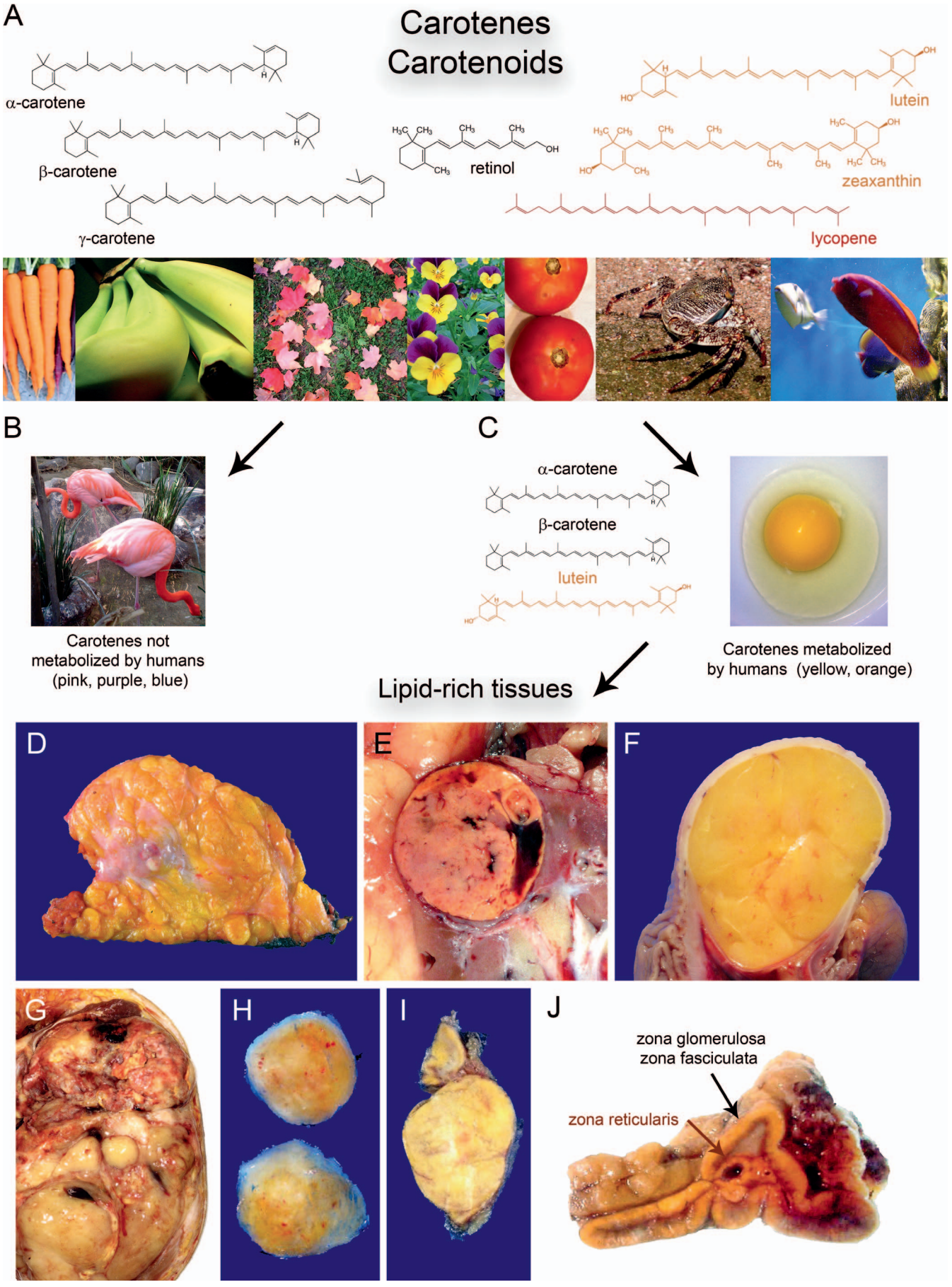
Figure 1. *A, Carotenes and carotenoids are unsaturated hydrocarbons derived from isopentenyl pyrophosphate and terpenes, which can only be produced by plants, where they are found in high concentrations. There are several carotene variants with a wide diversity of color. Young plants and fruits contain high levels of green chlorophyll that is degraded with age, exposing the color of the more-prevalent carotenes in them (yellow ripened fruit or orange-red leaves in autumn). Animals obtain carotenes from their diet, with each species able to metabolize only certain carotenes and not others. Carotenes are avidly lipophilic and are deposited predominantly in lipid-rich tissues. B, Flamingoes acquire their beautiful, pink-colored plumage from shells and fish they eat. C, Humans can only absorb certain carotenes (yellow, orange) that are present in plants and vegetables. A raw egg is an appropriate example to show how carotenes color cells yellow. The most-abundant carotenes in humans are α-carotene and β-carotene, lycopenes, and xanthines. Lipid-rich human tissues contain high amounts of yellow and orange carotenes, such as breast adipose tissue (D), clear cell renal cell carcinoma (E), submucosal intestinal lipoma (F), atypical lipomatous tumor/well-differentiated liposarcoma (G), schwannoma (H); adrenal cortical adenoma (I); and adrenal gland cortex (J). The 2 uppermost layers of the adrenal cortex are golden yellow (rich in aldosterone and lipids). However, the third layer or zona reticularis, contains high amounts of cytochromes and lipofuscin and is recognized as a thin brown line between the zona fasciculata and the adrenal medulla (gray). Retinol and xanthines are important for the retina (not shown).*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C
α-carotene
β-carotene
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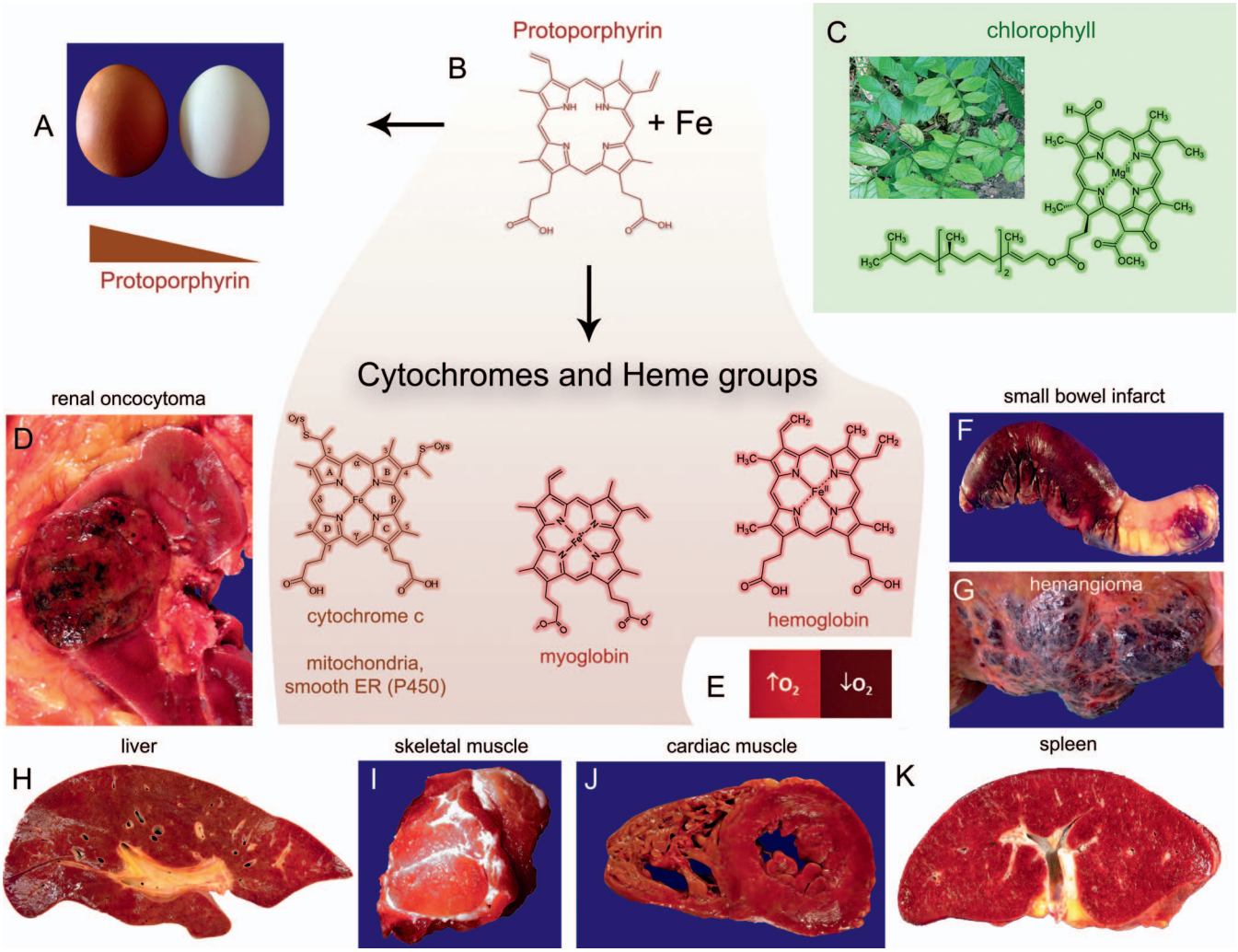

Figure 2. *A, The color of protoporphyrin can be appreciated in red or brown eggshells that contain high levels of this compound in contrast to white eggshells. B, Protoporphyrin is a ring molecule that results from the assembly of 4 pyrroles (colorless aromatic compounds that turn dark after contact with air). The attachment of iron (Fe) to the central portion of protoporphyrin generates a prosthetic group (or heme), which is the core component of cytochromes, certain enzymes, hemoglobin, and myoglobin. Ferrous iron (Fe^{2+}) is red-brown (rust), hence the color of these molecules. Cytochromes are predominantly located in mitochondria and smooth endoplasmic reticulum, either as single molecules (cytochrome c) or as part of large, enzymatic complexes (P450, complexes III and IV of the oxidative phosphorylation). C, Chlorophyll is another prosthetic group that contains magnesium instead of iron, which gives chlorophyll its characteristic green color. The human organs with the highest content of cytochromes are the kidneys and the liver. D, Tumors arising from these tissues, such as renal oncocytomas, have a red-brown or mahogany color. E, Hemoglobin (Hb) gives all organs a pink-red or dark-red hue, depending on the volume of circulating blood and oxygen (O_2) concentration. Congested blood in a small bowel infarct (F), and in a liver cavernous hemangioma (G) gives these tissues dark purple color (deoxygenated Hb). H, The liver is darker than the kidneys because of other pigments (see text). Myoglobin is a main component in skeletal (I) and cardiac muscle (J). The color of organs also results from the combination of cytochromes and Hb (spleen) (K) or myoglobin (heart) (J). For simplification, Hb and myoglobin are depicted only as a heme group without the globin chains.*

the best example of a lipid-soluble molecule with diverse functions, including vision, cell turnover of skin and mucosae, bone growth, and immune system homeostasis. There are probably several other functions of carotenes that are unknown.

Cytochromes, the Heme Group, Iron, and Bile Pigments

Pyrroles are heterocyclic aromatic molecules composed of a ring of 4 carbon atoms and one nitrogen atom (C_4H_5N).[1] Assembly of 4 pyrrole rings forms the tetrapyrrole ring protoporphyrin, a precursor of several organic molecules. Addition of a metal atom to the central portion of protoporphyrin results in the formation of an organic prosthetic group. This chemical structure, and more importantly, the type of metal atom attached, gives these compounds their color. Iron bound to protoporphyrin is red-brown like rust (heme groups). In contrast to eggs with white shells, the "rusty" color observed in pink or brown eggshells is due to protoporphyrin deposition (Figure 2, A and B).[12,13] In plants, magnesium bound to porphyrins generates the green pigment chlorophyll (Figure 2, C), and in marine arthropods and mollusks, 2 copper atoms bound to porphyrin form hemocyanin ("blue blood"), which acts as an oxygen transporter in these invertebrates. Hemocyanin

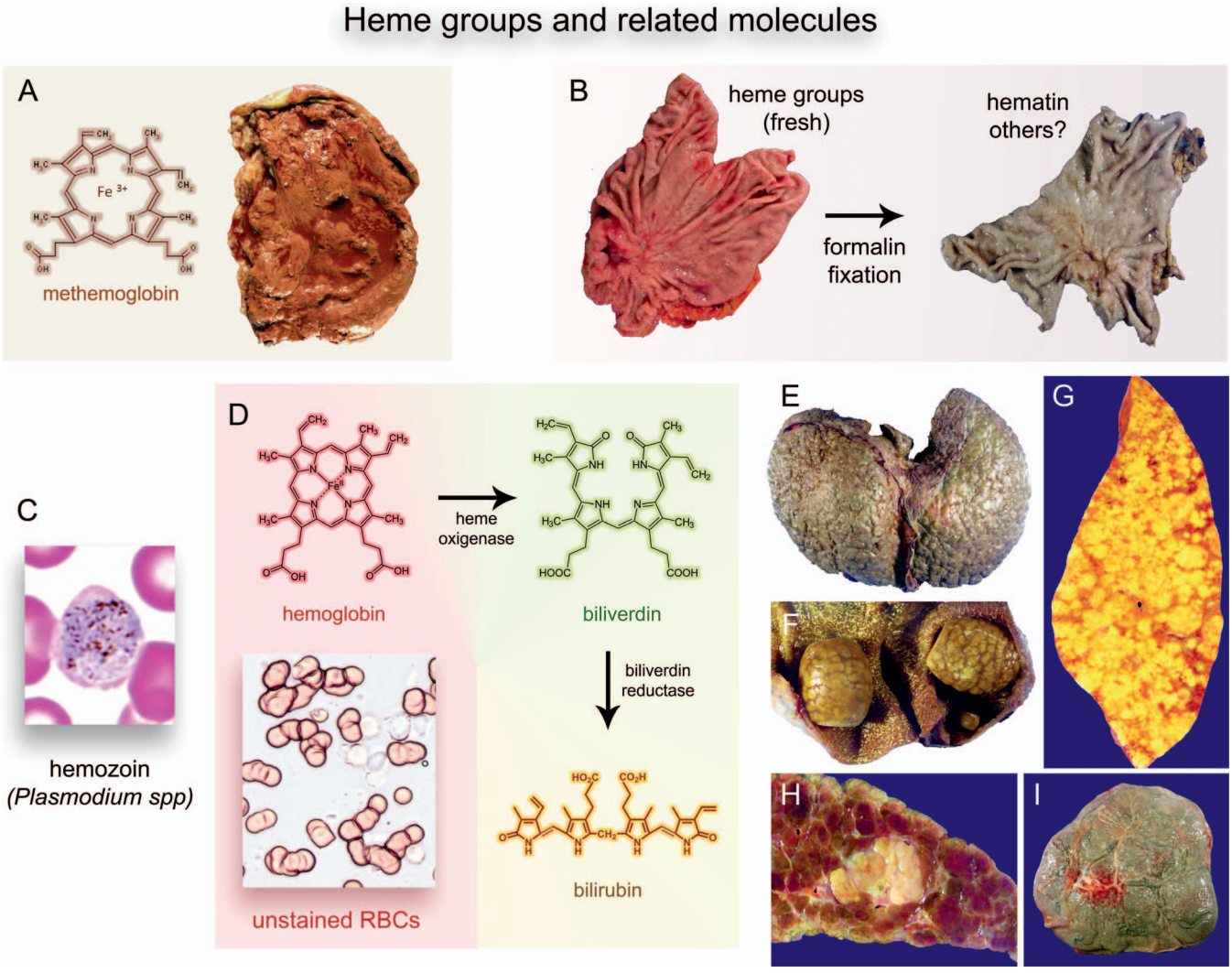

Figure 3. *Molecules related to heme groups (see text for details). A, Ferric iron (Fe^{3+}) gives methemoglobin (methb) a brown color, as shown in this opened endometriotic cyst. B, Formalin fixation alters the structure of heme groups and turns iron into Fe^{3+}, generating several intermediate compounds, such as blue-brown hematin, hence, the gray color of formalin-fixed tissues. C,* Plasmodium *spp metabolize heme groups into hemozoin within infected red blood cells (RBCs), which is the reason hemozoin should not be considered a "malarial pigment." D, Hemoglobin (Hb) is the principal component of RBCs. The natural red color of Hb is appreciated in an unstained peripheral blood smear. Free Hb is metabolized by macrophages into heme and globins, then to biliverdin, and finally into unconjugated bilirubin. The latter is transported to the liver and turned into conjugated bilirubin. Bilirubin is yellow-brown but may turn yellow-green after oxidation. Organs tinged by bilirubin include the cirrhotic liver (E) and the gallbladder with cholesterolosis and yellow-green gallstones (F). G, A slice of liver completely replaced by cholangiocarcinoma with common hepatic duct obstruction demonstrates the intense yellow coloration of tissues that occurs in obstructive jaundice. H, Hepatocellular carcinomas may also produce cholestasis and tinge the liver green-brown or yellow. I, Bile-tinged stools excreted by the fetus (meconium) color the placenta green-brown. For simplification, Hb and metHb are depicted only as heme groups without the globin chains (Wright stain, original magnification ×100 [C]; original magnification ×40 [D]).*

turns blue when oxygenated (like copper rust) but is colorless/transparent in a deoxygenated state. Cobalt, magnesium, and copper bound to porphyrins are found in such minimal amounts in humans that they do not exert any color effect.

Heme Groups.—Hemoglobin (Hb) and myoglobin are red because they contain heme groups. The degree of oxidation of the iron atom within these molecules determines the covalency and color of iron, that is, ferrous iron (Fe^{+2}) is red, whereas ferric iron (Fe^{+3}) is brown. Oxygenated blood and muscle are red because they contain Fe^{+2}. Oxygenated blood circulates throughout tissues giving all organs a pink-red hue,[14–17] more strikingly observed in the skin, mucosae, retina, the fresh gray matter of the brain, the red nucleus of the midbrain, the spleen, and the placenta. In contrast, deoxygenated blood is purple-blue because of its high carbamino-Hb content (CO_2 bound to Hb, purple-blue color) (Figure 2, D through K). Deoxygenated blood travels through veins and gives organs a purple-blue tonality ("cyanosis"). Hemorrhagic lesions will appear purple-blue for some time before the heme degrades, as seen in bruises, hemorrhages, hematomas, endometriotic cysts, cavernous hemangiomas, among others (Figure 2, F and G). In fair-skinned individuals, superficial veins appear blue-green from the visual effect of looking at purple-blue blood through a white-pink vessel wall, yellow fat tissue, and

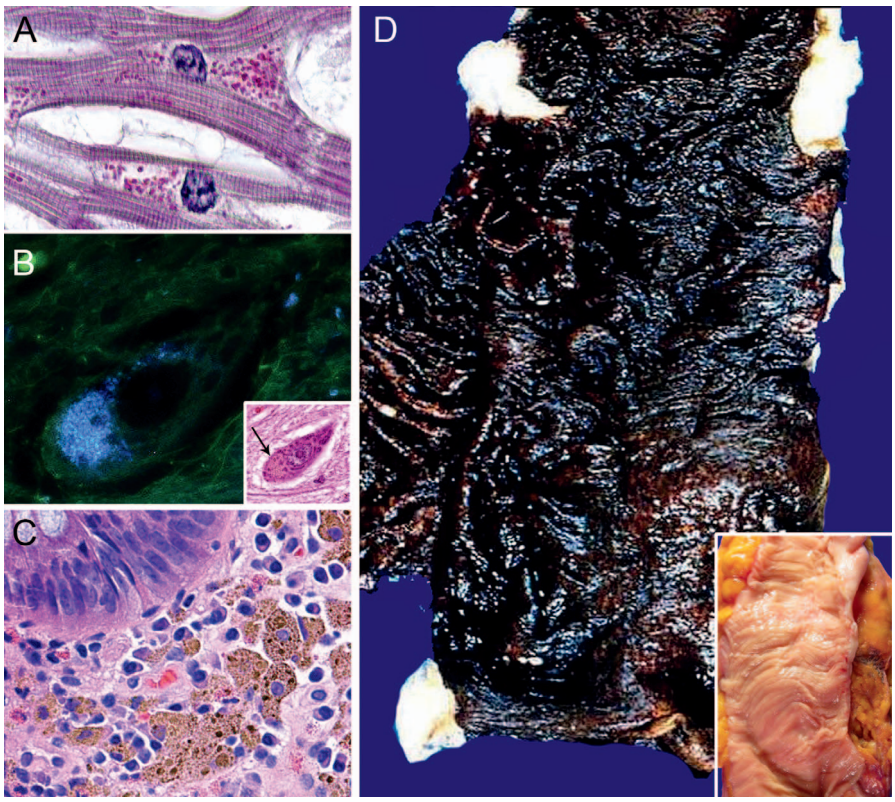

Figure 4. *Lipofuscin is a dark brown pigment that accumulates with age in several tissues but is often undetectable macroscopically. A, Cardiomyocytes with periodic acid–Schiff (PAS)–positive lipofuscin pigment adjacent to the nucleus. B, Neuron with lipofuscin observed under a fluorescence microscope; lipofuscin is autofluorescent. Inset, the arrow points to lipofuscin in the same neuron's cytoplasm. C, Microscopically, melanosis coli is seen as clusters of macrophages laden with lipofuscin (brown coarse granules) in the lamina propria of the colonic mucosa. D, Grossly, melanosis coli is reflected as a brown-black coloration of the colonic mucosa because of increased lipofuscin deposition secondary to excessive use of laxatives. Compare with the color of normal colonic mucosa (inset) (PAS, original magnification ×100 [A]; hematoxylin-eosin, original magnifications ×100 [B] and ×40 [C]).*

skin.[18] A low blood supply to tissues (anemia or volume redistribution) gives a characteristic "paleness" to all our organs. Carboxy-Hb (CO bound to Hb) has a higher affinity than oxygen for the heme group and gives Hb a cherry-red color. Similarly, nitric oxide (NO) binds myoglobin heme groups producing a pink-red hue in muscles and is the reason why NO is commonly used in the meat industry to maintain the "fresh look" of meats for long periods of time.[19] Blood and muscle containing Fe^{+3} are brown, as seen in devitalized muscles, methemoglobinemia, and deposits of old hemorrhage before the heme is metabolized (Figure 3, A).

Resected organs or tissues exposed to air after dissection change color slightly because of diffusion of CO_2 from Hb.[17] Changes in pH also appear to produce slight color variation in highly irrigated organs.[17] Tissues and blood turn brown-grey after fixation by the cross-linking effect of formalin and conversion of Hb into other compounds, including blue-brown hematin (Figure 3, B). Special chemical methods have been used to maintain or restore the red color (heme groups) of autopsy specimens after they have been fixed in formalin for long periods.[20,21]

Malarial parasites metabolize heme into the dark-brown pigment hemozoin (Figure 3, C), which enhances the virulence of *Plasmodium* spp and deposits in the liver as brown-black granules. Malarial organisms induce hemolysis and hemoglobinuria, hence the name "blackwater fever."

Enzymes that contain heme groups include myeloperoxidase, lactoperoxidase, and thyroid peroxidase.

Cytochromes.—These compounds can be found as single molecules (cytochrome *c*) or as part of large, enzymatic complexes that catalyze redox reactions, that is, photosystems I and II in the thylakoid membrane of chloroplasts, cytochrome P450 in the liver, and the electron-transport chain-reaction complex located in the inner mitochondrial membrane.[22] Because most cytochromes in humans contain iron, they are red or red-brown. Therefore, organs like the kidneys (proximal tubular epithelial cells) and liver (hepatocytes) with large numbers of mitochondria are red-brown. The liver is darker than the kidneys possibly because of the higher content in deoxygenated blood, bile pigment, and lipofuscin (discussed in the "Lipochromes" section) (Figure 2, D and H).

The most internal layer of the adrenal cortex (the zona reticularis) has a high content of smooth endoplasmic reticulum, mitochondria, and lipofuscin and is also red-brown. Close inspection of the adrenal gland shows this layer as a brown line located between the golden-yellow cortex (zona glomerulosa and fasciculata) and the gray-red adrenal medulla (Figure 1, J). Similarly, brown fat has a higher mitochondria content and is red-brown.[23]

The neoplastic counterparts of tissues with high amounts of mitochondria and/or cytochromes include tumors derived from kidney and liver cells; however, tumors with abundant mitochondria can be found at any location. Renal oncocytomas are typically laden with mitochondria and have a mahogany or dark-brown color (Figure 2, D). However, this color is not restricted to renal oncocytomas and can also be seen in some clear cell renal cell carcinomas and in chromophobe and papillary renal carcinomas that contain abundant mitochondria. In fact, any tumor with oncocytic features, such as, salivary gland and breast oncocytomas, Hürthle cell neoplasms, and pituitary adenomas (gonatroph, null cell), have a brown hue because of their high mitochondria content. Hibernomas, tumors of brown fat, show a mixture of red-brown and yellow colors. Liver tumors (adenomas or carcino-

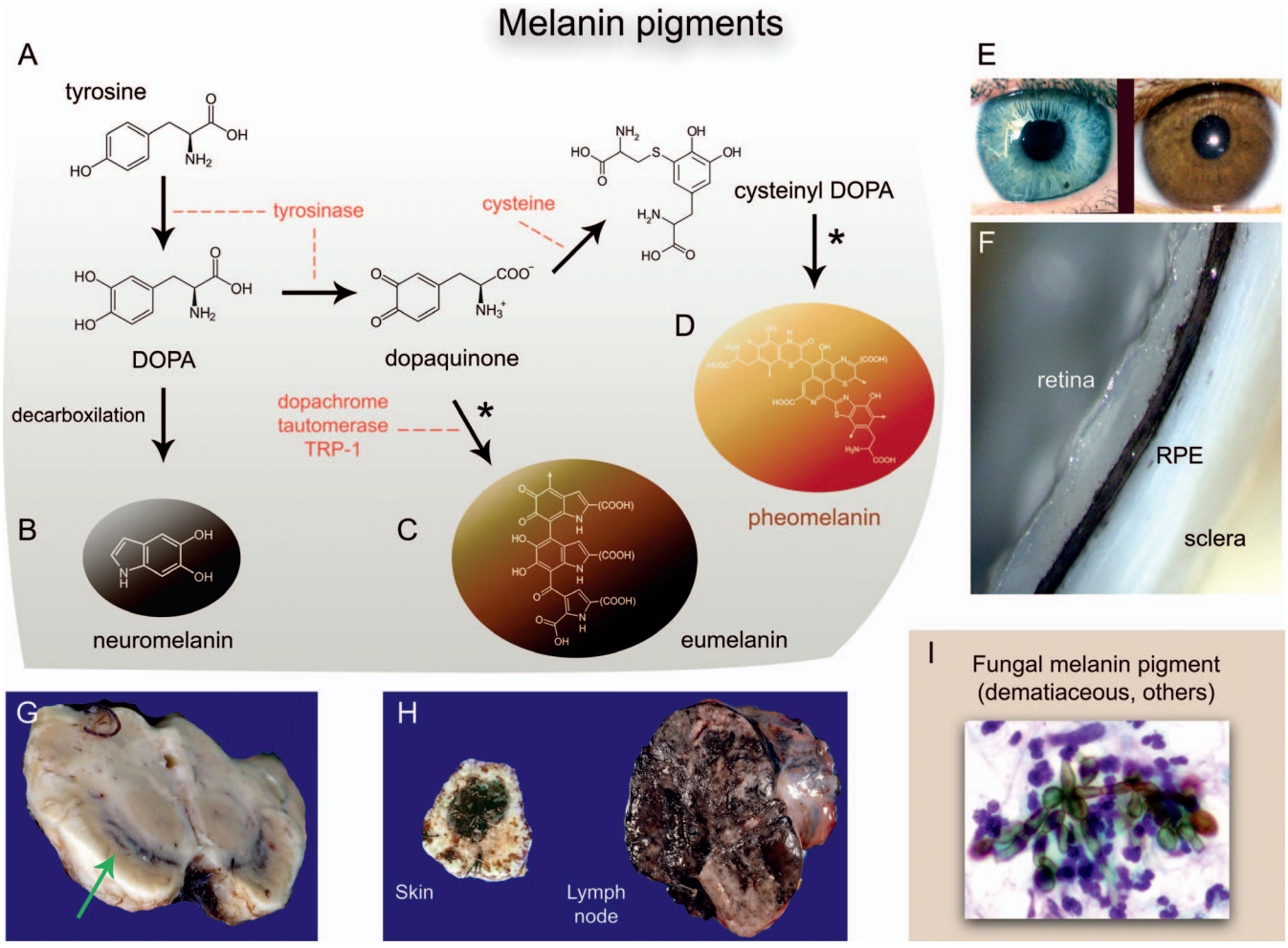

Figure 5. *A, Melanins are pigments derived from the metabolism of tyrosine converted to dihydroxyphenylalanine (DOPA) and dopaquinone. Humans produce melanin in 3 forms: neuromelanin (B), eumelanin (both brown-black) (C), and pheomelanin (golden yellow-red) (D). Intermediate compounds in the synthesis include indoles and quinones for eumelanin and benzothiazines for pheomelanin (*, not shown). Eumelanin and pheomelanin are represented as oligomers but are, in fact, large polymers (TRP-1, tyrosinase related protein-1.). D, Pheomelanin differs from eumelanin in its content of sulfur and cysteine. E, Eumelanin is the most abundant pigment in skin, appendages, and eyes, and its variable amounts and distributions produce the color variability in these human tissues (ie, blue or brown eyes). Pheomelanin is found at higher concentrations in red hair and the skin of lips and nipples (not shown). F, Eumelanin gives the brown-black color of the retinal pigment epithelium (RPE) in the eyeball, located between the retina (internal aspect of the globe) and the sclera (external aspect). G, Neuromelanin is found in the substantia nigra of the midbrain (arrow) and the loci coerulea (not shown). H, A cutaneous melanoma (left) and a melanoma metastatic to a lymph node (right) are brown-black because of the high content of eumelanin. Melanin pigments are also produced by fungi, which may give them virulence properties. I, Pigmented hyphae of* Scedosporium apiospermum *from a drained abscess at a port site on the chest wall (Papanicolaou, original magnification ×40).*

mas) usually resemble the dark-brown benign liver parenchyma.

Bilirubin and Iron.—Macrophages metabolize Hb to biliverdin and then indirect bilirubin, which is converted to direct bilirubin in the liver. Direct bilirubin is then secreted to intrahepatic bile ducts, stored in the gallbladder, and later secreted into the small bowel. Biliverdin is green (Latin *viridis* = to be green) and bilirubin is yellow-red (the suffix *-rubin* derives from the Latin *rubrum* = red) (Figure 3, D). Bilirubin gives a yellow-red color to the liver and tinges the gallbladder and biliary duct epithelia yellow-red (Figure 3, E and F). Once bilirubin is secreted into the small bowel, it is metabolized by bacteria into urobilinogen and stercobilinogen. These molecules are later catabolized to urobilin and stercobilin, which stain stools yellow-brown. Urobilinogen is reabsorbed into the bloodstream, filtered by the kidneys, and its catabolites are then excreted in urine giving it the characteristic yellow color. High concentrations of bilirubin look red-brown, as seen in a filled gallbladder, whereas less concentrated bilirubin in the blood or extracellular tissues tinges organs yellow (jaundice) (Figure 3, G). Acholia ("without bile" or pale stools) and choluria ("dark urine") occur in posthepatic jaundice because of an obstruction of bile secretions into the small bowel and increased secretion of bilirubin into the urine. The green color of bilirubin occurs after oxidation. Gallstones can be yellow, brown, yellow-green, or black depending on the proportion of lipids, cholesterol, and bile pigments (Figure 3, F). Hepatic adenomas or hepatocellular carcinomas with high amounts of bile may turn yellow-green or green-brown (Figure 3, H). The progression of colors seen in bruises, hemorrhages, or

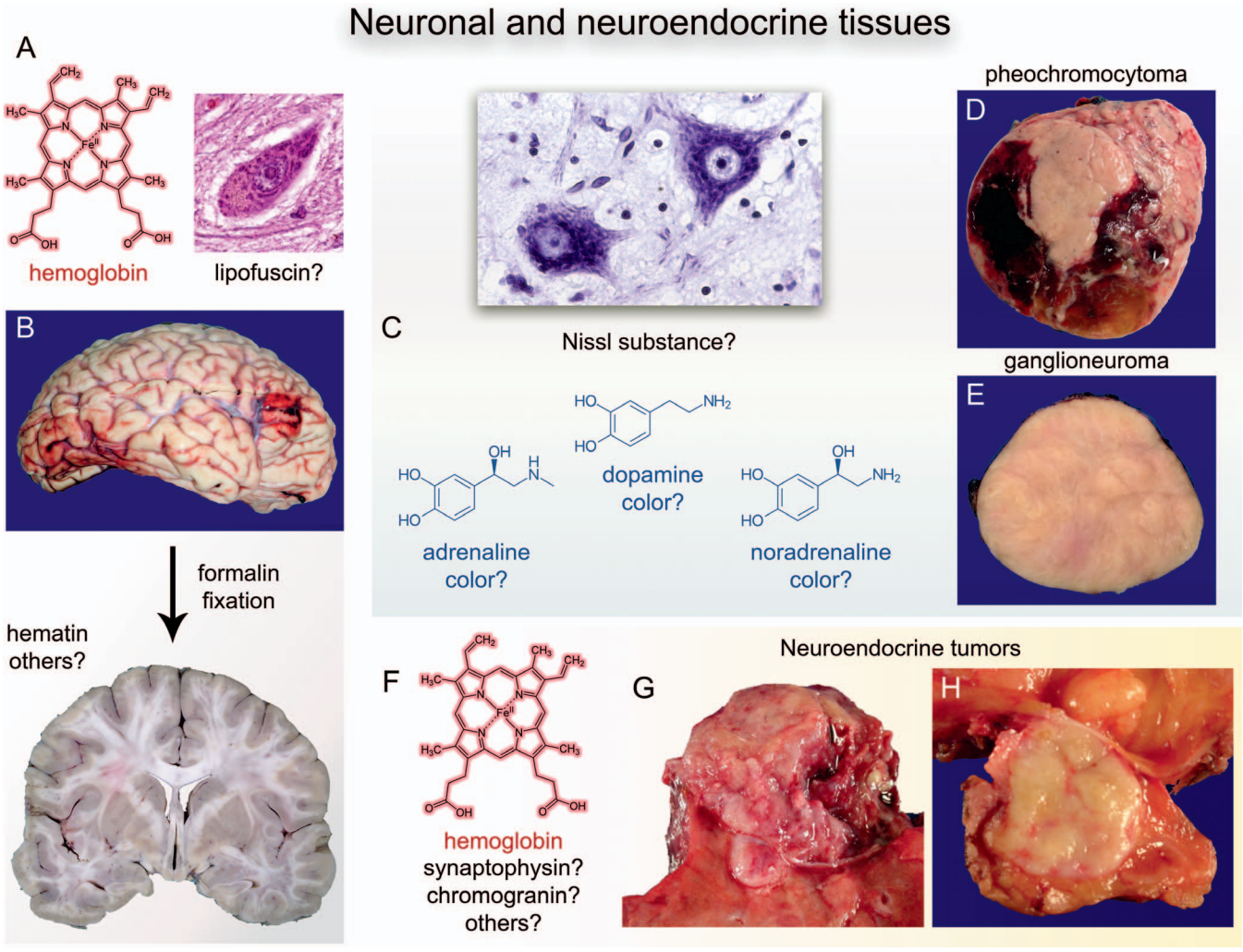

Figure 6. *A, The color of the brain gray matter is mostly derived from circulating blood and possibly from lipofuscin from neurons. B, The fresh encephalon has a pink-beige cortex that turns gray after formalin fixation (heme turned into hematin, see also Figure 3, B. C, However, it is possible that neurons have an intrinsic pink-beige color that could be derived from the Nissl substance, catecholamines, or other compounds, as is also shown in the similar color shared by, a pheochromocytoma (D) and a ganglioneuroma (E) with the fresh brain cortex. F, A similar situation could exist for neuroendocrine tumors that have a pale pink and/or yellow color, as shown in lung (G) and small bowel carcinoids (H) (hematoxylin-eosin, original magnification ×100 [A]; Nissl, original magnification ×100 [C]).*

hematomas from red to purple-blue, black, green, and yellow is explained by the conversion of Hb to deoxygenated Hb, heme catabolism to iron and protoporphyrin, and production of biliverdin and bilirubin, respectively. *Meconium* is the name given to green-brown stools that tinge the placenta and amniotic membranes green, which is sometimes associated with fetal-stress conditions (Figure 3, I). Meconium is composed of fetal intestinal secretions, bile (oxidized?), lanugo, and epithelial cells.

Iron that is not bound to porphyrins or cytochromes (found in hemosiderin and ferritin as Fe^{+3}) has a metallic gray-black color. When iron stores are extremely high in the body, the skin and organs turn gray-black, as seen in hemochromatosis patients or in individuals who receive chronic transfusions (aplastic anemia, thalassemia major, among others).

Lipochromes (Lipofuscin)

Lipofuscin (Latin *fuscus* = dark) is a pigment derived from the oxidation of lipids, which accumulates with age, predominantly in the heart, liver, retina, and brain (so-called wear and tear pigment) (Figure 4, A and B). The amount of lipofuscin found in these organs is not sufficient to cause dramatic changes in color—even in older individuals—but may give them a light-brown or beige tinge. For example, Leydig cells from the testis contain more lipofuscin as they senesce, which may be responsible for the darker color of the testicular parenchyma seen sometimes in older men.[24] Lipofuscin is also partially responsible for the brown color of the zona reticularis in the adrenal gland (Figure 1, J). The best condition to appreciate the dark-brown color of lipofuscin is melanosis coli ("black colon"), in which high amounts of lipofuscin—not melanin—are deposited in the colorectal mucosa after excessive use of laxatives (some lipofuscins are endogenous, whereas others are exogenous) (Figure 4, C and D). Because melanosis coli is not due to melanin pigmentation, the names pseudomelanosis coli or lipofuscinosis coli have been suggested. Lipofuscin deposits are also partly responsible for the rare condition known as

"black thyroid," which occurs in certain individuals after use of minocycline.[25] The thyroid turns brown-black, not only because of the deposition of the drug but also because lipofuscin accumulates within follicular cells. Both conditions are asymptomatic. However, increased deposition of lipofuscin in the retinal pigment epithelium is associated with the pathogenesis of age-related macular degeneration, and molecules that decrease lipofuscin in the retinal pigment epithelium may have a potential therapeutic role for this degenerative process.[26] Interestingly, the levels of lipofuscin from the olfactory lobes of the European lobster (*Homarus gammarus*) have been used as an age predictor for these crustaceans and for other marine animals.[27]

Melanin

Melanin (Greek *melanos* = black) is an intracellular pigment that results from the metabolism of tyrosine to dopaquinone (Figure 5, A). In mammals, it is produced by cells derived from neural crest and neuroectoderm, that is, melanocytes, eye pigment epithelium, and neurons. Melanin gives a wide spectrum of color to the skin, appendages, the eye, and certain structures in the brain. The color of these organs depends on the amount, distribution, and quality of melanin, which occurs in 3 forms: neuromelanin (brown-black), eumelanin (brown-black), and pheomelanin (golden yellow-red) (Figure 5, B through D).[28] Pheomelanin differs from eumelanin in its higher content of sulfurs and cysteine. Eumelanin is the major constituent of epidermal melanin, and its amount gives the variable color to black, brown, light brown, and blond hair, as well as fair, brown, and dark skin. In contrast, pheomelanin is present at higher concentrations in red hair and the skin of nipples, lips, and genitals.[28] Senescent follicular melanocytes decrease their production of melanin and eventually hair turns white. In the eyes, the proportion of eumelanin, pheomelanin, and capillary blood is responsible for the brown, hazel, gray, green, or blue color of the irides (Figure 5, E).[10]

Eumelanin and neuromelanin give a black color to the pigment epithelium of the retina (Figure 5, F), the substantia nigra ("black substance") in the midbrain (Figure 5, G), and the loci coerulea ("blue spots") in the pons. The loci coerulea receive their name from the blue color (*caeruleus* = blue, derived from the Latin word for sky, *caelum*) that results from the effect of looking at small black spots in a background of white myelin. The leptomeninges around the brainstem and spinal cord contain a variable proportion of meningeal melanocytes (higher in dark-skinned individuals), which gives meninges a blue-brown hue at these sites. "True" blue pigments do not exist in humans or any other animal.[29]

Benign and malignant neoplasms arising from melanocytes, that is, nevi and melanomas, are usually pigmented (Figure 5, H). A blue nevus results from the visual effect of looking at a brown-black dermal nevus through white soft tissues and skin. Studies have shown that dysplastic nevi can contain higher amounts of pheomelanin compared with eumelanin, which suggests a disruption of melanogenesis.[30] Increased vascularity (and perhaps increased pheomelanin) may be responsible for the red color seen in certain nevi, such as most Spitz nevi. By the same token, melanomas may become extremely dark, not only because of abundant eumelanin produced by the malignant melanocytes but also because of eumelanin accumulation within tumor-associated keratinocytes and dermal melanophages.[31] Melanoma cells have also been shown to aberrantly express macrophage enzymes that metabolize oligosaccharides in abnormal ways, promoting increased pigmentation.[31] Conversely, melanoma cells can lose their ability to produce melanin and become amelanotic. Primary amelanotic melanomas are pink because of their high vascularity. Metastatic melanomas, with variable levels of pigmentation, can look black, gray, or light brown (brown-black melanin combined with amelanotic pale pink tumor cells) (Figure 5, H).

What are the functions of melanins? Melanin pigments are crucial for animal life at all levels. They are involved in mechanisms of thermoregulation (lower vertebrates), camouflage, sexual attraction, and protection of the skin and underlying tissues from ultraviolet light (higher vertebrates).[28] In the eye, melanin turns the globus into a *camara oscura* ("dark chamber") to create the perfect environment for light perception. Melanin from the retinal pigment epithelium may also act as a chelator of toxic byproducts that result from the degradation of retinal. Neuromelanin is similar to eumelanin, but its function in the brain is only partially understood. Neuromelanin exerts neuroprotective effects by chelating metal elements and quenching reactive oxygen species that are toxic to dopaminergic neurons.[32,33]

Interestingly, melanin pigments produced by fungi (dematiaceous fungi, *Cryptococcus* spp, *Aspergillus* spp, *Candida* spp, *Penicillium* spp, among others) have a role in the survival and virulence of these organisms by interfering with the host immune phagocytic mechanisms (Figure 5, I).[5,34,35] Eumelanin is also the main component of the ink produced by coleoid cephalopods, that is squids (Teuthida), cuttlefish (Sepiida), and octopuses (Octopoda). Eumelanin is stored in an ink sac and released in several patterns (pseudomorphs, ink ropes, clouds, smokescreens, among others) and functions as a distractor to escape predation.[36]

Other Possible Pigments in Organs?

The central nervous system is composed of gray matter (primarily neurons) and white matter (primarily axons). The increased vascularity of gray matter structures (brain cortex and cerebral nuclei, cerebellar cortex and nuclei, brainstem nuclei, and spinal cord) confers a pink-beige color that turns gray after fixation (Figure 6, A and B). However, this pink-beige or gray color cannot be explained only by an increased blood supply (Figure 6, C). Ectopic brain tissue or tumors composed of neurons or neuronal-related elements, that is, gangliocytomas, ganglioneuromas, gangliogliomas, pheochromocytomas (Greek *phaios* = dark or black; from the chromaffin reaction), and macroscopic foci of mature brain tissue in teratomas, have a color reminiscent of gray matter (Figure 6, D and E). Therefore, we hypothesize neurons have an intrinsic beige or gray color. Because neurons contain high amounts of neurotransmitters (adrenaline, dopamine, among others), synaptic-associated proteins, rough endoplasmic reticulum (Nissl substance), and lipofuscin, it is possible that these elements contribute to the color of neuronal tissue. We could not find any information in the literature related to

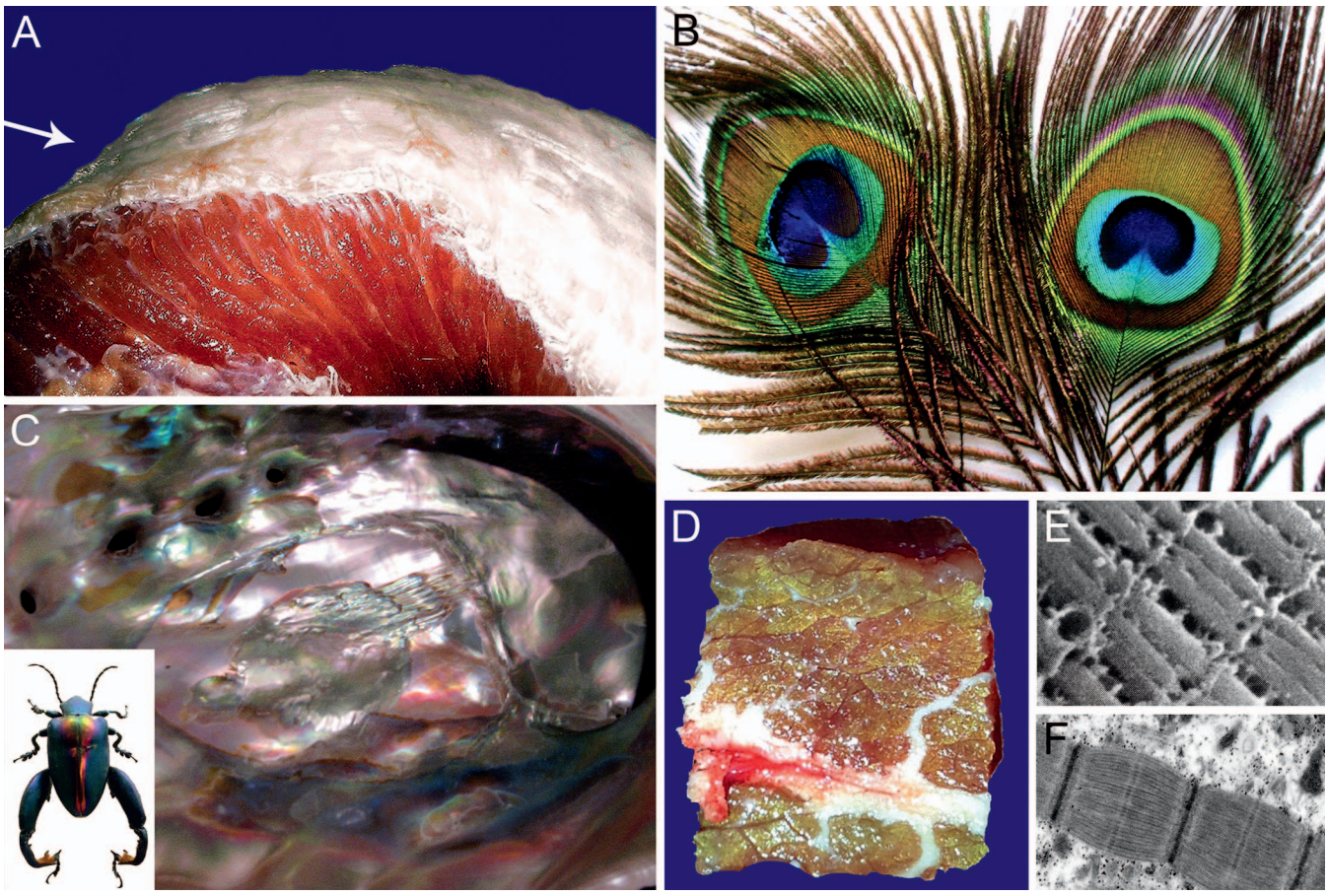

Figure 7. *Iridescence and structural coloration. Color by structure is not dependent on pigments but on the effect of light reflection and interference occurring on parallel-arrayed surfaces at the microscopic level. Structural coloration is long lasting and gives iridescence (pearly or metallic, multicolor coloration) to human tissues, including the aponeuroses, tendons, fasciae, and the dura matter. A, An area of white-silver iridescence (arrow) is observed in the overlying fascia of muscle. Iridescence can be readily appreciated in peacock feathers (B), nacreous shells (C), and beetle exoskeletons (C inset). D, Golden iridescence of cross-sectioned skeletal muscle fibers. Iridescence in skeletal muscle sections partially depends on the parallel array of myofibrils and myofilaments forming the sarcomeres, shown in a scanning electron micrograph (E) and a transmission electron micrograph (F) (impregnation with osmium tetroxide, original magnification ×11 500 [E]; uranyl acetate and lead citrate, original magnification ×8500 [F]).*

this matter. Another intriguing and unsolved question is, why are certain nuclei in the neonate brain particularly susceptible to the deposition of indirect bilirubin that causes kernicterus? (German *kern* = core or nucleus; Greek *ikteros* = jaundice). White matter color is discussed in the next section.

Neuroendocrine tumors, that is, carcinoids, are usually yellow, pink, or, sometimes, red because of hemorrhage (Figure 6, F through H); why carcinoids are this color is unknown. Do neurosecretory granules, chromogranins, or synaptophysin have yellow or pink color?

Iodine is an element that can look violet, yellow, red, or brown, depending on the solvent used[37]; when iodine is dissolved in water, it is yellow-brown. The thyroid is the only organ that contains high levels of iodine. Increased vascularity, in combination with the amount of yellow-brown iodine, gives the thyroid its color. Thyroid adenomas or carcinomas with high colloid content may remain red-brown but can also be white or pale pink because of an increased amount of epithelial thyroid cells (see the next section on carcinomas' white color). The parathyroids or parathyroid adenomas are pink from their high vascularity but may be light brown or red-brown when they contain prominent oncocytic changes.

Copper levels are too low in human organs to produce color, but in Wilson disease, the cornea shows an abnormal brown color from copper deposition (Kayser-Fleischer ring).

Ligaments are white to light gray but may also be yellow. The ligamenta flava (Latin *flavus* = yellow) are crucial for vertebral column support. This color is due to the intrinsic yellow color of elastin (not from carotenes).[38] Elastofibroma is a benign tumor composed of elastic fibers and fibrous tissue that has a typical yellow or sometimes gray color.

Smooth muscle in all organs (stomach, intestines, bladder, uterus) is pale pink. Contrary to skeletal and cardiac muscle, smooth muscle does not have a significant amount of myoglobin and is not red-brown. A comparable chromatic effect is seen in fish with pale-pink flesh (tilapia, *Oreochromis niloticus*) compared with fish with orange or red flesh (salmon, *Salmo salar*). Leiomyosarcomas retain the pink color of smooth muscle, but leiomyomas are

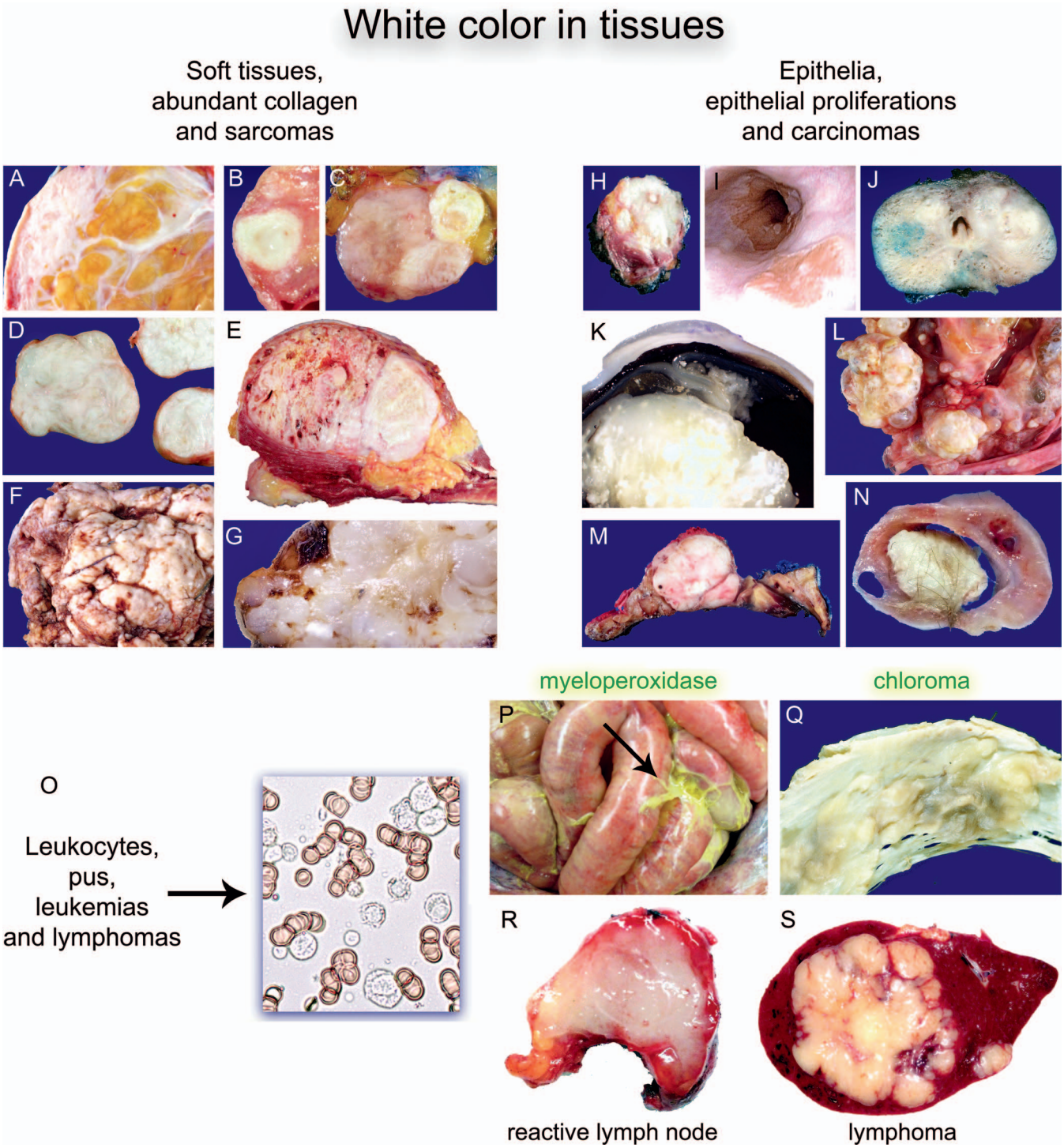

Figure 8. *An intrinsic white color is present in several organs. The possible reasons why these tissues are white are addressed in the text. Left panel: A, subcutaneous fibroconnective tissue in a case of lymphedema; B, a corpus albicans; C, 2 fibroadenomas (the smaller one is sclerosed and whiter); D, leiomyomata; E, high-grade sarcoma of the thigh; F, desmoplastic small round cell tumor; G, low-grade chondrosarcoma. Right panel: H, metastatic keratinizing squamous cell carcinoma to a neck lymph node; I, endoscopic image of the esophageal squamous mucosa with Barrett esophagus; J, prostatic adenocarcinoma (anterolateral solid-white nodules); K, retinoblastoma; L, mucinous cystadenoma with excrescences; M, thymoma; N, teratoma (cystic dermoid). Bottom panel: O, Leukocytes are colorless in an unstained peripheral blood smear in contrast to erythrocytes. Granulocytes contain myeloperoxidase, which is an enzyme with a heme group and a yellow-green color. In high quantities, myeloperoxidase is responsible for the yellow-green color of pus (P, arrow) and of this extramedullary (meningeal-based) myeloid sarcoma (Q), hence, the name* chloroma. *R, Reactive lymph nodes are white to pale pink because of their high lymphocyte content. S, Lymphomatous proliferations, such as a splenic diffuse large B-cell lymphoma, are also white likely because of the high content of deoxyribonucleic acid in the lymphoma cells (original magnification ×40 [O]).*

Table 1. Organs, Color, and Compounds That Produce Color

Organ or Tissue	Color	Biologic Pigment (From Most Predominant to Less Common)[a]
Blood		
Oxygenated	Red	Hb, ferrous iron
Deoxygenated	Purple-blue	Carbamino-Hb, ferrous iron
Skin and appendages		
Skin	Black, brown, yellow, white	Variable proportion of eumelanin, pheomelanin, and carotenes
Skin of nipples, lips, and genitals	Pink-red to red-brown	Pheomelanin, eumelanin, and carotenes
Hair	Black, dark brown, light brown, blonde, red, gray, white	Variable proportion of eumelanin and trichomelanin; gray and white hair, loss to lack of melanin; red hair, pheomelanin
Central nervous system		
Gray matter	Beige or gray	Hb, lipofuscin? Unknown intrinsic color in neurons?
White matter	White	Myelin, sphingolipids
Substantia nigra	Black	Neuromelanin
Loci coerulea	Blue-black	Little neuromelanin in a myelin background
Pituitary gland	Pink or light brown	Hb, cytochromes (oncocytic changes)
Dura and leptomeninges	White	Collagen
Brainstem and spinal cord leptomeninges	May be blue-brown (dark-skinned individuals)	Collagen and variable proportion of eumelanin
Peripheral nerves and nerve roots	White	Myelin, sphingolipids, and collagen
Eye		
Choroid, RPE	Brown-black	Eumelanin
Iris	Dark brown, brown, hazel, green, blue, gray, rarely violet	Eumelanin, pheomelanin, Hb
Retina	Orange-red	Hb, carotenes, retinol, lipofuscin?
Macula lutea	Yellow	Carotenes: lutein and zeaxanthin
Sclera	White	Collagen
Cornea, lens, and vitreous humor	Transparent/colorless	None
Mucosae	Pink-red	Hb in blood vessels
Tongue and all skeletal muscles	Red or pink	Myoglobin, Hb, cytochromes, carotenes?
	Iridescence in cross section	Structural color, not pigment
Teeth and enamel	Pearly white	Calcium phosphate
Salivary glands	Pink, light brown with or without yellow hue	Carotenes (from fat), cytochromes, Hb
Thyroid	Red-brown	Hb, iodine
Parathyroids	Pink, may be light or dark brown	Hb, cytochromes (oncocytic changes)
Thymus	Pale pink to yellow	Carotenes (from fat), Hb, others?
Lungs	Pink	Hb, cytochromes?
	Purple	Hb and anthracotic pigment
Heart	Red-brown	Myoglobin, cytochromes, Hb, lipofuscin, and carotenes?
Liver	Red-brown, dark brown	Cytochromes, carbamino-Hb, bilirubin, lipofuscin, carotenes?
Gallbladder, bile ducts		
Mucosa	Yellow tinge	Bilirubin
Smooth muscle	Pink	Little myoglobin, Hb, unknown?
Spleen		
Red pulp	Dark red	Hb, cytochromes, hemosiderin (iron), carotenes?
White pulp	Pale yellow to white	WBCs white color, others?
Pancreas	Pink to yellow	Carotenes (from fat), cytochromes, Hb
Esophagus, stomach, small bowel		
Mucosa	Pink-white	Epithelia intrinsic white color? Underlying Hb in submucosa
Smooth muscle	Pink	Little myoglobin, Hb, unknown?
Large bowel		
Mucosa	Pink-white	Epithelia intrinsic white color? Underlying Hb in submucosa
	Yellow-brown tinge	Urobilinogen and stercobilinogen
Smooth muscle	Pink	Little myoglobin, Hb, unknown?
Adipose tissue		
"White" fat	Bright yellow	Carotenes
Brown fat	Light brown	Carotenes and cytochromes
Adrenal glands		
Zona glomerulosa and fasciculata	Golden yellow	Carotenes and aldosterone
Zona reticularis	Brown	Cytochromes, carotenes, and lipofuscin
Medulla	Gray-red	Norepinephrine or epinephrine?
Kidneys	Pink-brown	Cytochromes, Hb, carotenes?
Bladder and ureters		
Mucosa	Pink-white	Epithelia intrinsic white color? Underlying Hb from submucosa

Table 1. Continued

Organ or Tissue	Color	Biologic Pigment (From Most Predominant to Less Common)[a]
Smooth muscle	Pink	Little myoglobin, Hb, unknown?
Gonads		
Testes	Pink to light brown	Hb, white color of germ cells? Lipofuscin from Leydig cells?
Ovary	Pink-red	Hb, cytochromes? others?
Corpora lutea	Golden yellow	Carotenes
Corpora albicantia	White	Collagen, others?
Uterus and fallopian tubes	Pink	Little myoglobin, Hb, unknown?
Cervix	Pearly white to pink	Epithelia intrinsic white color?
Superficial veins	Blue-green in fair-skin individuals	Effect, purple-blue, carbamino-Hb; white-pink, vessel walls, overlying fat, and skin
Ligaments	Gray-white to yellow	Intrinsic yellow color of elastin (ligamentum flavum) Autofluorescence
Bones	White	Collagen, others? Autofluorescence
Cartilage	White, bluish to semitranslucent	Collagen, others?
Tendons and fasciae	White Iridescence	Collagen, others? Structural color, not pigment
Serosal and amniotic membranes	White to translucent	Epithelia (mesothelium, amnios), intrinsic white color? very little collagen stroma?
Lymph nodes, tonsils	Pale pink	WBCs white color, Hb, others?
Stromal bone marrow	Red-brown	Combination of Hb from RBCs and WBCs white color, cytochromes?
Placenta	Purple-red	Combination of Hb from RBCs, cytochromes? Carotenes?
Umbilical cord Wharton jelly	White	Mucopolysaccharides, collagen (not type I)

Abbreviations: Hb, hemoglobin; RBCs, red blood cells; RPE, retinal pigment epithelium; WBCs, white blood cells.

[a] Question marks (?) indicate a theory or possibility.

typically white because of the high content of white collagen (see below).

Rudolph Virchow originally coined the term *amyloid* (Greek *amyloid*; Latin *amylum* = starch) in the 19th century. Amyloid was erroneously considered a starch or fat-derived material because of its yellow-white color and waxy appearance, hence, the comparison of amyloid deposits in organs to fat, bacon, or lard ("lardaceous" liver or spleen). Amyloidosis is also known as "Wilks disease," in honor to Samuel Wilks, who not only used the term *lardaceous* disease but also coined the eponym of Hodgkin disease in the 1850s to 1860s. We now know that amyloid is composed of deposits of abnormal immunoglobulins, transthyretin, among others, but the reason why amyloid has this particular color is unknown.

PRODUCERS OF WHITE COLOR IN HEALTHY AND NEOPLASTIC TISSUES

Calcium Phosphate

Calcium (Latin *calcis* = lime, Ca^{+2}) is one of the most abundant minerals on Earth. Elemental calcium is metallic gray, but when combined with other elements, it turns into white calcium carbonate ($CaCO_3$) or white calcium phosphate ($CaPO_4$). Seashells are white because they are made of calcium carbonate, whereas white eggshells are made of calcium phosphate. As mentioned previously, eggshells can also be pink or brown as a result of the accumulation of red-brown protoporphyrins synthesized within the egg (Figure 2, A). Like eggshells, mammalian bones and enamel are white because they are mostly composed of $CaPO_4$ (see below). However, human bones or teeth do not commonly turn pink or brown, unless there are unusually high levels of protoporphyrins, as seen in the very rare porphyrias. In these diseases, bones and teeth can turn yellow-orange and exhibit red fluorescence (erythrodontia; Latin *erythros* = red) (see also fluorescent pigments section). A long list of extrinsic and intrinsic substances can cause bone and teeth discoloration but are beyond the scope of this review.

Like normal bone and enamel, bone matrix- or enamel matrix-producing tumors, that is, osteoid osteomas, osteoblastomas, osteoid-producing osteosarcomas, odontomas, odontogenic tumors, and ameloblastomas are white, particularly in areas with $CaPO_4$ matrix deposition.

Other White Molecules and Iridescent Organs

Several organs, tissues, and cells in the human body are white for unknown reasons. They include soft tissues (collagen), epithelia, myelin, platelets, and leukocytes (Greek *leukos* = white). We hypothesize that these tissues lack color because (1) they cannot absorb carotenes or only absorb minute amounts that macroscopically do not affect color; (2) they do not have abundant mitochondria or cytochromes; (3) they have very high contents of deoxyribonucleic acid, which is intrinsically white (lymphomas, leukemias, and small round cell tumors are made of cells with high nuclear to cytoplasmic ratio); (4) they are avascular or require minimal blood supply; and (5) they do not contain melanin, lipofuscin, or any other pigments (intrinsically white).

Soft Tissues, Collagen, and Iridescence.—Type I collagen is the most abundant protein in animal soft tissues and is composed of banded fibers (tropocollagens) with a transverse periodicity. Bone, cartilage, tendons, fasciae, aponeuroses, the eye sclerae, the tunica albuginea,

Table 2. Compounds Causing Color in Abnormal and/or Neoplastic Tissues

Biological Pigment	Features/Colors	Diseases or Neoplasms[a]
Carotenes	Not produced by humans, obtained from the diet	Lesions and tumors with high content of fat
α-carotene and β-carotene Lycopenes Xanthines (lutein, zeaxanthin) Retinol (vitamin A) Others?	Yellow to orange (in humans) with variable intensities	*Benign:* Xanthomas, orange palpebral spots, orange tonsils (Tangier disease), carotenemia (xanthoderma), lycopenemia, lipomas, fibrolipomas, lipoleiomyomas, schwannomas, adrenal cortical adenomas, steroid cell tumors, fibrothecomas, or any benign tumor with abundant adipose tissue *Malignant:* Well-differentiated liposarcomas, adrenal cortical carcinomas, clear cell RCCs, or any malignant tumor with abundant adipose tissue
Prosthetic groups (protoporphyrin ring + metal atom)	Originally derived from metabolism of amino acids and pyrroles, porphyrin synthesis in mitochondria	Tumors with high content of mitochondria or cytochromes necessary for redox reactions
Heme and cytochromes: protoporphyrin + iron	Red-brown	*Benign:* Renal oncocytoma, hepatic adenoma, hibernoma (also carotenes), oncocytic tumors in other organs: salivary gland (oncocytoma, Warthin tumor), ACTH-producing pituitary adenoma, Hürthle cell adenoma, some parathyroid adenomas? *Malignant:* Some RCCs and HCCs, some neuroendocrine tumors? Carcinoids? GISTs? Some sarcomas?
Other cytochromes: protoporphyrin + copper (enzymatic cofactors)	Brown, only in rare conditions from copper overload	Wilson disease: cornea (Kayser-Fleischer ring)
Hb: heme + globins (Fe^{+2})	Red Pink hue	Recent hemorrhage or bruise Several tumors with variable degree of vascularity and blood supply
Carbamino-Hb: Hb + CO_2	Purple-blue	Recent hemorrhage or bruise, organ congestion, hemorrhagic infarct, endometriosis, benign and malignant vascular tumors (angiomas, angiosarcomas, Kaposi sarcoma); hemorrhagic tumors (choriocarcinoma)
Heme variants: met-Hb	Brown	Methemoglobinemia, necrotic tissues, hemorrhagic tissues with Fe^{+3} before Hb degradation
Heme metabolites		
Biliverdin (macrophages)	Green	Bruises after several days
Bilirubin (liver)	Yellow-red	Bruises after several days, jaundice, choluria, cholestasis, gallstones, kernicterus (basal ganglia and olivary nuclei, indirect bilirubin) *Benign liver tumors:* Adenomas, focal nodular hyperplasia *Malignant:* HCCs with cholestasis, metastatic HCCs?
Other metabolites		
Hematin	Blue-brown	Tissues after formalin fixation
Hemozoin (erroneously referred as *malarial pigment*)	Brown-black Heme metabolized by *Plasmodium* spp	Malaria infection, black granules in liver, and other organs (brain)? "Blackwater fever" (hemolysis, hemoglobinuria, and possibly hemozoin)
Meconium (bilirubin, lanugo, fetal epithelial cells, others)	Green-brown (oxidized bilirubin?)	Meconium-tinged amniotic membranes, umbilical cord, and placenta
Myoglobin (similar to Hb)	Red-brown Pink-red (white and red brown)	*Benign:* Rhabdomyoma, myoglobinuria from rhabdomyolysis *Malignant:* Rhabdomyosarcomas (high-grade component white)
Myeloperoxidase (dimeric enzyme with heme prosthetic group)	Yellow-green intrinsic color? or the result of chlorinated product after phagocytosis?	*Benign:* Abscesses and acute inflammation *Malignant:* Leukemias, myeloid sarcomas/chloromas

Table 2. Continued

Biological Pigment	Features/Colors	Diseases or Neoplasms[a]
Iron	Brown-black, bound to hemosiderin or ferritin, ferric state (Fe^{+3})	Bruises or hemorrhages, several days after the catabolism of heme into iron and biliverdin
		Markedly congested spleen (brown, Gamna-Gandy bodies), endometriosis (so called "blueberry spots"), PVNS
		Hemosiderosis (acquired) chronic transfusions with iron overload and iron deposition in several organs (heart, liver, pancreas, pituitary gland, among others)
		Hemochromatosis (genetic)
		Malignant: HCC with high iron content
Lipofuscin and other lipochromes	Brown-black	Color of heart, brain, liver, testes in the elderly?
	Autofluorescence	Melanosis coli (pseudomelanosis or
	Known as "wear and tear" pigment	lipofuscinosis coli) partly endogenous and exogenous from laxatives
		Black thyroid (also minocycline deposition)
		Age-related macular degeneration
		Some Leydig cell tumors; other tumors?
Melanins		
Eumelanin	Brown-black	Variable amount in nevi, leptomeningeal melanosis, primary melanomas (cutaneous, mucosal, uveal), metastatic melanoma, clear cell sarcomas of soft tissues, pigmented DFSP (Bednar tumor), pigmented MPNST?
Pheomelanin	Golden yellow-red	Increased in some dysplastic nevi, Spitz nevi?
Neuromelanin	Brown-black	Decreased/absent in Parkinson disease, other neurodegenerative diseases?
Intrinsic neuronal pigment?	Unknown	
Catecholamines, acetylcholine, dopamine, synaptophysin, chromogranin or Nissl substance? Lipofuscin?	Beige or gray	*Neuronal-derived:* Tubers, gangliocytomas, ganglioneuromas, gangliogliomas, foci of mature brain tissue in teratomas; pheochromocytomas (true color is pink-beige; dark red is from hemorrhage)
	Pale-pink, yellow	*Neuroendocrine:* Carcinoids, paragangliomas
Retina (neuroectoderm)	White	Retinoblastoma
Elastin	Yellow or gray-white	Elastofibroma
Amyloid	Yellow-white	Amyloidosis (Wilks disease): Amyloid deposition in several organs depending on the subtype; most commonly due to paraproteins (immunoglobulins from PCN)
Calcium phosphate	White, bone and enamel matrix	*Benign:* Osteomas, osteoblastomas, odontomas *Malignant:* Osteosarcomas, ameloblastomas
Unknown		
Intrinsic type I collagen color?	White	*Benign or indeterminate:* Scars, fibrosis, desmoid tumors, leiomyomas, fibroadenomas, any collagen-producing tumor
	White, semitranslucent	Enchondroma and chondrosarcomas
	White, pale pink (with Hb), light brown (with red-brown cytochromes)	*Malignant:* Synovial sarcoma, high-grade sarcomas, undifferentiated sarcomas; GIST? MPNST?
	White, pale yellow (with yellow fat from carotenes)	High-grade areas in liposarcoma
Intrinsic epithelial cells color? Keratins, keratohyaline granules, intercellular edema?	White	*Benign:* Keratoses, leukoplakias, hyperkeratotic lesions, epidermal inclusion cysts and dermoid cysts contents, plaques of psoriasis (also iridescent)
	White or pale pink (from Hb in blood vessels)	*Malignant:* Basically all carcinomas (squamous carcinomas, adenocarcinomas, small cell carcinomas)
Intrinsic leukocytes color? High DNA content?	White	Lymphomas, leukemias, small blue round cell tumors, poorly differentiated tumors
	Tumor composed of cells with high nuclear to cytoplasmic ratio	
Intrinsic color of myelin?	White	Diffuse gliomas, nerve sheath tumors
Fluorescent		
Porphyrins	Yellow-orange to red in daylight	*Porphyrias:* Very rare genetic diseases; brown teeth and bones, porphyrinuria
	Pink-red fluorescence in ultraviolet light	Erythrodontia, fluorescent bones, skin lesions, plasma, urine, and stools

Abbreviations: ACTH, adrenocorticotropic hormone; DFSP, dermatofibrosarcoma protuberans; Fe^{+2}, ferrous iron; Fe^{+3}, ferric iron; GIST, gastrointestinal stromal tumor; Hb, hemoglobin; HCC, hepatocellular carcinoma; MPNST, malignant peripheral nerve sheath tumor; PCN, plasma cell neoplasms; PVNS, pigmented villonodular synovitis; RCC, renal cell carcinoma.

[a] Question marks (?) indicate a theory or possibility.

and the corpus albicans are white (Latin *albus* or *albicans* = white). The particular arrangement of collagen fibers in tendons and fasciae also causes these anatomic structures to be iridescent (Figure 7, A). Iridescence is because of structural coloration, a phenomenon caused by light interference and light reflection effects that occur on the surface of thin films or surfaces "structured" in parallel patterns that generate a metallic multicolor effect.[39] Structural coloration does not depend on pigments. Examples of structural coloration and iridescence can be appreciated in the shiny brilliant colors of peacock (*Pavo cristatus*) feathers, butterfly (Rhopalocera) wings, the exoskeleton of beetles (Coleoptera), the skin of fish and cephalopods, and the fruit of the African plant marble berry (*Pollia condensata*) (Figure 7, B and C).[39–41] Structural coloration is also crucial for the brilliant blue colors in several organisms[39] and may also be seen in sectioned skeletal muscle from mammals (Figure 7, D through F). Type II collagen is white and is the main constituent of cartilage. Because of the high contents of water and proteoglycans, cartilage may look translucent or bluish. Another example of the white color of soft tissues is the umbilical cord, which is composed predominantly of mucopolysaccharides (Wharton jelly). The abundance of pigments within any of these white tissues can tinge them different colors: hemosiderin, brown; bilirubin, yellow; meconium, green-brown.

Benign and malignant proliferations of fibroblasts, smooth muscle, or stromal cells that produce type I collagen are white, such as old scars, leiomyomas, and several sarcomas ("fish-flesh" appearance) (Figure 8, A through E). However, the color of these white lesions may vary depending on the proportion of blood vessels (pink or red; vascular tumors), fat (yellow; liposarcomas or schwannomas), and mitochondria and cytochromes (light brown). Low-grade sarcomas with so-called areas of dedifferentiation are usually white. High-grade sarcomas, desmoplastic small blue round cell tumors (Figure 8, F), and dendritic cell sarcomas are white. Curiously, gastrointestinal stromal tumors are pink or light brown for unknown reasons. Benign and malignant neoplasms of cartilage (enchondromas or chondrosarcomas) retain the translucent or bluish coloration of the cartilage matrix (Figure 8, G) with high-grade sarcomatous components being recognized as solid, white lesions.

Epithelia.—All epithelia are avascular and intrinsically white, without melanin pigmentation. This situation can be observed in patients with albinism, who have white skin and hair, as well as red irides (colored only by blood in the iris capillaries). In addition, the intrinsic white color of epithelia can be seen in benign and malignant epithelial proliferations, such as the plaques of psoriasis (which may show iridescence because of structural coloration), keratoses, epidermal inclusion cyst, and dermoid cyst contents, oral leukoplakias, and basically, any carcinoma (Figure 8, H through N). The white color produced by a squamous epithelial proliferation appears not to depend exclusively on the thickness of the resulting keratin layer because it takes a keratin layer of only 10 to 20 μm to produce a white lesion.[42] However, several mucosae and skin sites have the same thickness and are not white. Perhaps abnormalities in keratin or the keratohyaline granules and/or modifications of the intercellular milieu induce changes that make epithelia look white.[42] A comparable phenomenon occurs when we spend long hours in water, and the skin of the fingers turns wrinkled and white because of epidermal intercellular edema, or the color difference between the white lunula and the transparent nail plate because of the quantity of sulfur compounds. Thymomas are epithelial tumors that can be rich in fat, epithelial cells, and lymphocytes and have a yellow or pale-pink color (Figure 8, M). Carcinomas with high intracellular lipid content (usually clear cell under the microscope) may be yellow. Fibroepithelial lesions are also pale pink to white.

White Blood Cells.—Leukocytes and tumors arising from these cells, such as leukemia ("white blood") and lymphomas, are also white (Figure 8, O). Myeloperoxidase is an enzyme found in azurophilic granules of neutrophils (and less in monocytes) that also contain heme, but rather than being red-brown, it is yellow-green. This is the reason why abscesses and pus (collections of granulocytes rich in myeloperoxidase) have a yellow-green color (Figure 8, P). When leukemias form a mass at extramedullary sites (myeloid sarcoma), the high content in myeloperoxidase of the neoplastic myeloid cells gives these tumors a yellow-green hue, hence, the name chloromas (Figure 8, Q). Reactive lymph nodes are pale pink to pink-white because they mainly contain lymphocytes (Figure 8, R). Like sarcomas, lymphomas are also referred to as having a fish-flesh appearance (Figure 8, S). Granulomas are composed of macrophages and do not typically contain granulocytes; they are also white to pale pink if not associated with other pigments (hemosiderin, anthracotic pigment).

Others.—As mentioned previously, myelin remains white despite the concentration of carotenes in the body. Diffuse gliomas expand the white matter and infiltrate and efface the brain gray matter, which losses its typical pink-beige or gray color. High-grade gliomas are pink or red because of increased vascularization and/or necrosis. Seminomas are white or occasionally pale pink because of increased vascularity. Seminoma cells lack pigments and are rich in glycogen, which is colorless.

Transparent or colorless organs include the cornea, the lens, and the vitreous humor. The cornea and lens are avascular and possess delicate cellular mechanisms to remain water free to keep their transparency. When these mechanisms fail, the cornea or lens turns white, as occurs in corneal edema, keratitis, or cataracts. Long-standing cataracts turn brown from previous hemorrhages.

PRODUCERS OF FLUORESCENCE IN TISSUES

Fluorophores or fluorochromes are molecules that emit light in a longer wavelength than the one that excited them. Lipofuscin, elastin, and collagen have intrinsic fluorescence that is not strong enough to be observed at a macroscopic level (Figure 4, B).[38,43] As mentioned previously, porphyrias are rare genetic diseases associated with impaired porphyrin metabolism that result in the accumulation of fluorescent porphyrins in organs. The severity of these diseases depends on the type of enzymatic deficiency and the accumulated metabolite. In the exceedingly rare congenital erythropoietic porphyria (uroporphyrinogen III synthetase deficiency), the stools and urine turn

dark red (porphyrinuria) and bones and teeth acquire a yellow-orange color. The accumulated type I porphyrins in secretions and tissues emit an impressive pink-red fluorescence under ultraviolet light.[44,45] The fluorescent properties of porphyrins can also be seen in the fox squirrel (*Sciurus niger*). This rodent has an asymptomatic form of congenital erythropoietic porphyria, and its bones also exhibit pink-red fluorescence under ultraviolet light, identical to the bones and teeth in humans affected by this type of porphyria.[46]

Table 1 summarizes the human organs or tissues and the biologic pigments that give them a particular color. Table 2 summarizes the compounds that cause color in abnormal and/or neoplastic tissues.

CONCLUSIONS AND UNANSWERED QUESTIONS

The variation of color in the human body has always intrigued curious minds and is possibly the reason why a "Humorism theory" was prevalent in ancient times. The 4 humors were linked to 4 tissue origins, 4 elements, and 4 colors: blood (heart/air/red), yellow bile (liver/fire/yellow), black bile (spleen/earth/black), and phlegm (brain/water/gray-white). Any imbalance in these "humors" was associated with disease.[47] We now appreciate that colors in living organisms are the result of complex biochemical reactions with the production of biologic pigments (cytochromes, porphyrins, melanins, lipochromes) or because of structural coloration (iridescence). Carotenes are only produced by plants but are acquired by animals through their diet. The function of biologic pigments is only partially understood, with most available information coming from studies in plants, microorganisms, cephalopods, and vertebrates but, unfortunately, not humans. In general, biologic pigments have antioxidant and cytoprotective effects. Recent discoveries also point to pigment production as an evolutionary advantage in pathogenic microorganisms.[5] Although abundant information is available on the ultraviolet-protective effects of melanin and the function of cytochromes and heme groups, the role of other biologic pigments in human organs is still uncertain. Several questions remain to be answered, such as, What other functions do carotenes have in our organs? What other functions does neuromelanin have in the brain? Do we have colorless cytochromes or porphyrins in our body, and, if so, what are their functions? Why are certain tissues white? Methylene blue is used to treat methemoglobinemia, and hematin and carotene derivatives are used to treat porphyrias. Do any pigments exert antimicrobial or therapeutic effects? Do pigments in tumors differ biochemically from pigments in their nondiseased tissue counterparts, and if the answer to that is yes, could that lead to potential targeted therapies for cancer in the future? The effects of metabolism on cancer are currently a hot topic in oncology. Because pigments are strong antioxidants, we hypothesize that some of these molecules could have potential therapeutic effects (direct or indirect) on tumors or, perhaps, increase the effectiveness of current antineoplastic therapies. All these questions remain unanswered and represent a blank page in the book of science that, hopefully, will be written upon by future scientists and physicians.

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