PIGMENTATION OF THE HIND-GUT

A PATHOLOGIC AND EXPERIMENTAL STUDY*

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The presentation of a paper based on the observation of a small number of cases must justify itself by dealing with a rare condition or by demonstrating new facts concerning a well known subject. With the advance of intestinal surgery, and the increasing number of "developmental reconstructions" and other operations which involve removal of the cecum and part or all of the first portion of the hind-gut, we are able to note with more frequency a pigmentation or melanosis of the mucosa of both organs. This pigmentation may or may not be transitory; but the rarity of its observation at the necropsy table, and the fact that at times a fading of color may be noted through the proctoscope, lead to the supposition that, in not all cases at least, is it macroscopically permanent.

PATHOLOGY

Gross Pathology.—Both the gross pathology and the histopathology of pigmentation of the hind-gut have been so clearly given by Pick that any subsequent description of the tissue changes observed must of necessity follow him closely in detail if not in phraseology. Macroscopic appearance of the intestinal mucosa in pigmentation of the hind-gut not only varies with the amount of pigment present, but is evidently influenced to a certain extent by the manner in which the tissue is handled. In tissue removed at operation, the color is materially affected by congestion which follows clamping, and in three cases here cited pigmentation was revealed only by microscopic examination. This factor may to some extent be responsible for the infrequent recognition of pigmentation of the hind-gut at time of operation and divert such tissue from the laboratory to the furnace of the unscientific hospital. In such portions of the hind-gut as may be observed by means of the proctoscope, the color varies from gray-black to light brown, or it may have the mottled "toad's back" appearance mentioned by Pick. Two specimens of the present series which were removed at operation and included the ileocecal valve, cecum and ascending colon were uniform gray-black or mottled throughout. Pick has described the mucous membrane as being mottled like a toad's back, and noted the following variations in color: "The tint may become a little lighter in diffuse spots of the mucosa, or in an entire segment, passing from a deep black into a lighter shade of brown." He further notes that there may or may not be a failing of melanosis toward the rectum. On these minor points my observations are not entirely in accord with those of Pick. In the one case seen at necropsy there was an even tar-black pigmentation from ileocecal valve to rectum; in the other cases, even shading throughout the specimen. It is natural that the influence of postmortem change should be thought of, but the specimen of this series was secured within two hours after death, and it is

not probable that such a factor would be overlooked by Berlin's most astute pathologist. A cut section of the intestinal wall may show a thin brown or black line corresponding to the mucosa, or the surface may exhibit nothing indicative of pigmentation. There is variation in thickness from that of tissue paper to somewhat more than normal. Extreme thinness is confined to the cecum and is, of course, a condition frequently noted in long standing cases of intestinal stasis. The serosa shows no change. In Case A, the mesenteric glands of the mesocolon were darkened. In Case A, the abdominal organs, as in the cases of Pick and other observers, were free from pigment.

Microscopic Pathology.—When the intestinal wall has markedly thinned, there is, of course, a diminution in the depth of the gland pits; otherwise they appear to maintain their normal depth. The cells lining the glands may be somewhat increased in size, they may present a normal appearance, or they may be somewhat smaller than normal. The goblet cells are neither increased or diminished in number, nor do cells foreign to this layer appear. The connective tissue of the mucosa is not affected except in the very thin intestines, where it appears to have undergone some degree of atrophy. In the connective tissue of the mucosa, between the basement membrane of the gland epithelium and the muscularis of the mucosa, are observed a varying number of pigment cells. These cells may be arranged in a uniform layer and lie close to and follow the basement membrane of the epithelium, or scattered through the stroma of the mucosa. The cells vary in size from 7 to 20 microns and have a single round or oval concentric nucleus. Such pigment as they contain is not uniform either in size of granules or in color. Some cells are gorged with large light or dark brown granules, while others hold dust-fine, saffron-colored particles. There is also a certain amount of free pigment in the form of isolated granules or clumps of granules, though the clumps of granules may be pigment cells so overloaded with pigment as to obscure their cell bodies. The pigment cells resemble morphologically the plasma cell found normally in this locality, though Pick considers them connective tissue cells of the tunica propria, and Henschen and Bergstrand regard them as several types of the wandering class of connective tissue cells of the stroma of the mucosa. Sections of two ileocecal valves showed pigment to stop at a midpoint in the valve, the ileac side being pigment free. Large numbers of eosinophils may at times be seen in the mucosa, and in Case A an occasional ameboid-looking body was noted, but the character of these bodies could not be determined. The last tissue examined exhibited pigmentation of the distal end of the ileum.

Submucosa: In several cases pigment cells were found in the solitary lymph nodes, and occasionally a cell can be seen beneath the muscularis, which is in contradistinction to the description of Pick, but has been noted by Henschen and Bergstrand. The muscular walls and serosa were free of pigment cells, and neither I nor my colleague, Dr. Jeffries, could note microscopic change worthy of mention other than occasional atrophy. Mesenteric glands: In Case A, pigment cells corresponding in every way with those of the mucosa could be seen. These cells appeared to be principally gathered on one side of the gland in a position probably corresponding to the junction of the afferent duct.

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* Because of lack of space, this article is abbreviated in THE JOURNAL. The complete article appears in the Transactions of the Section and in the author's reprints.

Chemical Examination.—It would be of no avail to chronicle in detail a series of failures. All solvents and dyestuffs which I could think of, or which were suggested by the experiments of others, gave negative results. Hence, if deduction can be drawn from negative results, the pigment, from its resistance, must resemble the melanin group.

NATURE OF THE PIGMENT

Pigments relating to intestinal pigmentation fall naturally into two groups—exogenous and endogenous. Of exogenous pigments but little need be said, they being, as a rule, salts of either silver or mercury, easily accounted for in the clinical history of the patient and demonstrated without difficulty by chemical and microchemical methods. Endogenous pigments present a much more difficult problem for consideration, and it is practically impossible to confine such considerations to any specific pigment or group of pigments. Von Gierke¹² says one can divide endogenous pigments into two great groups, those derived from blood pigment (hemoglobin pigments) and those formed from other body substances through cell activity (autogenous pigments). If one follows the classification of Heuck, endogenous pigments encountered in the body may be divided into the hemoglobin pigments and the autochthonous pigments. Further subdivision separates the hemoglobin pigments into three groups, malarial pigment, hematoidin and hemosiderin. The autochthonous pigments include the fat-containing abnutzungspigment and the melanin. In contradistinction to the classification of Heuck, and as illustration of the diversity of opinion on the subject of body pigments, may be quoted the following somewhat broad definition by Adami.¹³ In the paragraph dealing with "modified hemoglobin," Adami speaks of a succession of modifications of the hemoglobin pigment "hematin," leading to the eventual deposit in tissue of two, or more correctly, three substances, hematoidin, hemosiderin and hemofuscin. Further, Stengel and Fox¹⁴ say that consideration of hematogenous pigment "concerns the deposition of pigments derived from hemoglobin, of which there are two groups, the siderous and the non-siderous. The chief siderous pigment is hemosiderin, which has, however, many modifications; the non-siderous pigments are derivatives of hematin-hema-

toidin, hemafuscin, melanin, etc." Heuck, on the other hand, does not think that hemosiderin is derived from hematoidin, nor does he consider hemofuscin one of the pigments coming from coloring matter of the blood but rather belonging to that class of pigments originating from lipid substance and in consequence being an abnutzungspigment identical with the lipofuscin of Borst. As to the derivation of melanin or melanins, von Furth, according to Adami, regards them as being developed by the action of intracellular oxidases (tyrosinase) on the aromatic chromogen group of the protein molecule.

As it is not necessary here to regard malarial pigment, the chemical composition of only two of the blood pigments need be considered, following the classification of Heuck. Concerning the exact nature of these pigments and the chemical processes involved in their formation there is much controversy. Their

characteristics in general, however, are as follows: Hematoidin is a red or brownish gold, crystalline or granular substance, dissolved in concentrated sulphuric and nitric acids and distorted by alkalis; its iron reaction is negative. Hemosiderin is a golden yellow to brown, granular or flaky substance, soluble in acids but insoluble in alkalis; its iron reaction is positive. The definition of abnutzungspigmenten or lipid pigments given by von Gierke is that by such are understood a class of granular, golden brown pigments that give a lipid reaction. As illustrations he mentions pigment found in heart muscle, liver, seminal vesicles, etc., which may be normally present or occur in diseased tissue. Heuck describes it as a golden brown, flaky substance insoluble in acids or alkalis; its iron reaction is negative; it is always positive

Fig. 1.—Pigmentation of the ileum: A, A, gland; B, B, pigment cells; C, muscularis mucosa; D, submucosa; pigment cells in submucosa. (Photograph by Dr. Wightman.)

to basic dyes and irregularly positive to fat dyes. Hammersten,¹⁵ in writing of melanins, says that there are some forms which are slightly soluble, and others easily soluble, in alkalis. He mentions choroid pigment as an example of sulphur-free melanin. Others mention melanin as a substance containing a minimal amount of iron but a relatively considerable quantity of sulphur. According to Heuck's table, melanin is a substance occurring in the form of brown crystals or flakes; it is insoluble in acids and alkalis and does not take any stains which are used for the identification of abnutzungspigment.

For the identification of pigments, one must consider the morphologic, microchemical and staining

12. Von Gierke, E., in Aschoff, Ludwig: *Pathologische Anatomie*, 1911, 1.

13. Adami, J. G.: *Principles of Pathology*, 1910, 1.

14. Stengel and Fox: *A Textbook of Pathology*, 1915.

15. Hammersten, Olaf: *A Textbook of Physiological Chemistry*, Mandel, 1900.

characteristics. Morphologic characteristics include form and color of pigment substances. Microchemical reactions pertain to solubility in acids and alkalis of varying strengths and at different temperatures which may be applied for a few minutes or allowed to act for several months. Staining characteristics are ascertained by treatment (both before and after tissue has been subjected to the action of acids and alkalis) with the basic dyes, Nile blue and neutral red, and the various dyes for the differentiation of fats such as are mentioned by Schmorl,¹⁶ or in any similar book which deals with chemical and microchemical methods of treating tissues. Summed up, the information one obtains concerning the nature of pigments found within the intestinal wall is based principally on three factors, namely, the solubility of the pigment, its iron content, and its ability to take dyestuffs both before and after treatment with acids, alkalies and other chemical substances.

THEORIES CONCERNING INTESTINAL PIGMENTATION

Limiting this matter to the views of those men who have had the most extensive opportunities for observation of pigmentation of the hind-gut, it is necessary to consider only the opinions of Solger, Pick, Heuck, Henschen and Bergstrand, and Lynch.

Solger appears to have been influenced to a marked extent by the location of the pigment, which he noted as confined exclusively to the tunica propria of the mucosa, the solitary follicles being spared. Although the reactions for iron yielded no very clear results, he considered it necessary, on the basis of the microscopic picture, to assume that the pigment was derived from blood chromatin, especially on account of the resemblance of the pigment deposits to the granular cells observed in the surrounding bloody deposits. Topographic relation of the pigment deposits corresponded with the vascular distribution, more particularly of the small veins. Hence the assumption of stasis in these vessels as a probable cause of pigment formation, though why pigment should show a predilection for the mucosa of the large intestine was not clear.

Pick agrees with Solger as to the distribution of pigment. He, however, noted that it was for the most part contained within cell bodies, and on this is based the hypothesis of his theory of pigment production. By microchemical tests Pick was able to exclude iron from the composition of intestinal pigment, but the presence of iron and a not inconsiderable quantity of sulphur was indicated by microchemical examinations. According to his experiments, the pigment did not appear to be a blood derivative in its chemical properties but to belong rather to the class of true melanins. The melanins of melanosis of the large intestine originate, according to Pick, from the aromatic albumin-disintegration products of the contents of the large intestine (indol, skatol); under the influence of an oxidative ferment, resembling tyrosinase, produced by the connective tissue cells of the mucosa. The capacity for production of this ferment is apparently individual. Indol and skatol are transformed into true melanin, in the connective tissue cells, by way of absorption in the mucosa. This interpretation renders intelligible the otherwise inexplicable limitation of the disease to the large intestine, on the one hand, and to the mucosa with its connective tissue cells, on the other.

Heuck agrees with Solger as to the pigment location and notes, as did Pick, the pigment cells. He considers the condition a true melanosis, and was able in one instance to examine an intestine which exhibited both true melanosis and pseudomelanosis. The pigment he assumes to be "propigment" between true melanin and lipofuscin, though perhaps more closely allied to the latter. It is, as he thinks, a fat pigment normally present in the intestine and increased in quantity through the action of some unknown agent. Why it should be confined to the large intestine, or as to the nature of the pigment cells, he expresses no opinion.

Henschen and Bergstrand consider the pigment to be between a true melanin and abnutzungspigment. They do not agree with the foregoing observers regarding either the limitation of pigment to the large intestine or to the mucosa of the large intestine. In one or two cases noted by them, pigment was found not only in the solitary follicles but also in the glands of the mesocolon. Pick's theory of pigment formation by connective tissue cells of the tunica propria does not appeal to them as a tenable one. Chronic obstipation being an almost invariable symptom, they regard it as an important etiologic factor. Their supposition is that on the hypothesis of absorption or elimination the etiology of the condition will eventually be worked out.

The theory of Lynch is interesting not only from its variance with those before considered, but because it is the result of deductions drawn from a study of the literature on the subject up to the article of Heuck, combined with opportunity for observation of the living tissue. Lynch, who prefers the term "hemachromatosis" for the designation of intestinal pigmentation, says he is inclined to think that "hemachromatosis is of bacterial origin; that the extent of the disease is dependent upon the severity of the infection; that the probable source of infection is the intestinal tract, possibly starting as an intestinal putrefaction; that this putrefaction lowers the vitality of the tissues, and thereby the cells of the mucous membrane lose their protective properties; consequently bacteria find ready access to the portal circulation. As a result of this, the chromogenic function of the liver is interfered with, and the liver becomes surfeited with pigment and is not capable of abstracting iron from the hemoglobin, with the result that an excessive amount of pigment is circulating in the blood. Further, the cells of the intestine probably have a selective action for these pigments, and as a consequence they are deposited in the tissue, etc. These pigments may or may not give a reaction for iron."

ETIOLOGY OF INTESTINAL PIGMENTATION

The theory of Solger, in view of subsequent researches by Pick, Heuck, Henschen and Bergstrand, hardly appears to merit consideration. Plausible as at first seem the hypotheses of Pick, they will hardly bear analysis. It is well known that indol (Combe¹⁷) is produced in the small intestine, and although Pick was without doubt aware of this fact, he must, to make his contention of the limitation of pigment to the hind-gut plausible, assume indol to be an exclusive product of the large intestine. That indol is not an important etiologic factor is indicated by the rarity of pigmentation in the terminal portion of the ileum

16. Schmorl, G.: *Untersuchungsmethoden*, 1914.

17. Combe, A.: *Autointoxication*, States, 1908.

where indol and skatol are produced in large quantities. Henschen and Bergstrand are not able to understand, and with reason, why, even if the first part of Pick's theory were correct, he should assume a connective tissue cell of the tunica propria to be elected for the complicated metabolic process of pigment making. They contend that not a single cell, but several cells of the wandering type of connective tissue cell, are the ones in which pigment is seen. Their supposition is based on variation in the shape of the cell bodies and on the presence of more than one nucleus in some cells. Neither Pick nor I have been able to note other than mononucleated pigment cells, nor could any variation in the form of cell bodies be considered due to other than distortion by pigment granules.

Concerning the nature of pigment, opinion does not diverge as widely as would seem apparent at first glance. With the exception of Lynch, all agree that it does not appear to be a blood pigment. Pick, Heuck, Henschen and Bergstrand agree that it resembles a melanin, and Heuck and Henschen and Bergstrand consider it of the abnutzungs class between melanin and fat-containing pigment. Heuck thinks that it resembles more the latter. In this status it will probably remain until new or more refined methods of chemical analysis can be applied to this particular problem.

There is some degree of satisfaction in the contemplation of conclusions regarding the nature of intestinal pigment. Unfortunately, not so much comfort can be derived from theories concerning its etiology. When one considers the problem, it resolves itself into the following questions: What is the nature of the pigment; what produces it; why is the pigment confined principally to the mucosa of the hind-gut; why is the pigment contained principally in cells; why is chronic obstipation an almost invariable accompaniment of pigmentation? Concerning the first question there is nothing to add to the exhaustive analyses of Heuck and Henschen and Bergstrand, and that the pigment substance belongs to a group between the true melanins and the fat-containing pigments appears conclusive. That a ferment is active in pigment production is in accord with the theory of Pick and not entirely at variance with the opinions of Henschen and Bergstrand, who incline toward an absorption or excretion theory. In considering absorption and secretion as factors, it is, so far as our present knowledge of the function of the hind-gut is concerned, reasonable to assume that absorption plays a more important rôle than secretion. It must not be forgotten, however, that though the physiologists tell us that secretions from the hind-gut

contain no distinctive enzymes and are composed principally of water, it has been clearly demonstrated by Draper¹⁸ and others that under abnormal conditions intestinal mucosa is capable of assuming utterly foreign secretory functions. In support of the absorption factor is the possible action of a variety of decomposition products from putrefactive processes which are accentuated by chronic obstipation. These processes, while usually pronounced in the cecum and hind-gut, may, under certain conditions, be also present in the terminal portion of the ileum. That the substance responsible for the production of pigment in the hind-gut is related in a measure to the so-called tyrosinase, is, in view of the proved nature of intestinal pigment, a not illogical conclusion. The fact that the condition is principally confined to the large intestine supports the assumption that conditions for the production of the tyrosinase-like body are most favorable in that locality. I believe that

putrefaction of the contents of the cecum and hind-gut, so invariably an accompaniment of chronic intestinal stasis, is the most important contributing factor. This assumption is based not only on the fact that chronic obstipation is almost without exception observed in individuals whose colons exhibit pigmentation, but also on the statement of Lynch that he had noted a diminution of the optically visible pigment to be coincident with relief of chronic obstipation, and, in consequence, permanent acceleration of the fecal current. I further consider it probable that the pigment-producing ferment is formed principally in the cecum, and that pigment is manufactured by such intestinal mucosa as comes into contact with and absorbs this ferment. Henschen and Bergstrand have shown that part of the ileum may

Fig. 2.—Pigmentation of gland of mesocolon: A, normal tissue; B, pigment cells; C, granular nature of pigment. (Photograph by Dr. Wightman.)

be pigmented, and I have examined two such tissues. Both intestines were removed from individuals that had numerous peritoneal adhesions which confined the distal portion of the ileum in such a manner that stagnation of the fecal current took place to a degree usually confined to the cecum and hind-gut.

Involvement of the cecal half of the ileocecal valve would further strengthen the view that only such mucosa as comes into contact with the pigment-forming ferment will be found to contain pigment. It does not, however, seem probable that this ferment has an intracellular action. It is more probable that it acts on the intercellular substance, of which there is a comparative abundance in this locality. Such an assumption in a measure accords with the conten-

18. Draper, J. W. (Maury): *Am. Jour. Med. Sc.*, 1909; *Experimental Intestinal Obstruction*, *THE JOURNAL A. M. A.*, Oct. 21, 1911, p. 1338.

tion of Heuck that we are merely observing an increase of a normally present pigment. From the position of the vast majority of pigment cells it would appear that the ferment acts with rapidity on the first intercellular substance which it encounters after passing the basement membrane. In support of this theory it must be remembered that in the mucosa of the cecum and hind-gut we are not dealing with as highly specialized tissue as that of the liver or of the kidney, but with a tissue whose even passive function has been considered by some as anatomically and physiologically nonessential. As the cecal and colonic mucosae are practically passive walls through which fluids pass, it is more probable that the action of the pigment-producing ferment is on intercellular substances and fluids and not on intracellular substance of any cell or group of cells. The variation in pigment building capacity mentioned by Pick should depend more on duration and intensity of stasis than on difference of individual property to produce pigment-forming enzyme. This is supported by the statements of Henschen and Bergstrand regarding the number of pigmented intestines they encountered in individuals past 40, and by my experience with intestines removed because of chronic intestinal stasis.

Pigment cells are, in my opinion, plasma cells which have acquired visible phagocytic properties. These cells are found in considerable numbers in the stroma of the mucosa; and the cells studied appeared to be morphologically nearer the plasma cell than any other found in the locality. By arrangement of the pigment-containing cells, it would appear that the plasma cells attempt to follow the action of the white cells, which become phagocytes, and to form a protecting wall against further invasion by pigment-producing enzyme, in addition to removing the pigment. Were it possible to follow microscopically the change accompanying permanent acceleration of the fecal current, one could no doubt observe, coincident with decrease of pigment-forming enzymes, a gradual assimilation of pigment granules, as suggested by the experience of Lynch. Migratory properties of the plasma cell carry it to different parts of the connective tissue stroma, and at times to and beyond the muscularis. Those pigment cells seen in the solitary follicles and in lymph nodes of the mesocolon may be accounted for by the migratory properties of the cell or by the effort of the lymphatic system at removal of waste products.

The theory of Lynch is so at variance with that of other writers that it must be considered apart. It should be of material interest to the reader because of the unusual opportunity for the clinical observation on which it is partially based. I, however, cannot consistently reconcile Lynch's idea of the effect of bacterial infection with the number of nonpigmented but severely infected hind-guts which I have had the privilege of examining for him. Furthermore, it is difficult to understand why a selective action for intestinal pigments should be conferred almost uniformly on cells of the connective tissue stroma of the hind-gut.

REPORT OF CASES

SERVICE OF DR. LYNCH

CASE 1.—Mrs. M., aged 45, had had obstipation for ten years. An operation for developmental reconstruction was performed. Tissue examination revealed pigmentation confined to the mucosa of the hind-gut. The solitary nodules were pigment free. There was no change in other intestinal walls.

CASE 2.—Mrs. O., aged 50, exhibited symptoms which Dr. Lynch associates with pigmentation of the hind-gut. There was prolonged constipation, toxemia, urine at times free from indican, and blood in the stools. Proctoscopic examination revealed ocher-colored pigment extending from the anus to the sigmoid. Tissue examination of bit snipped through the proctoscope revealed pigmentation of the mucosa. The appendix exhibited pigmentation of the mucosa.

SERVICE OF DR. DRAPER

CASE 3.—Mrs. R., aged 44, had severe hemicrania averaging fifty a year, together with severe congenital constipation. An operation for developmental reconstruction was performed. Tissue examination revealed pigmentation confined to the mucosa. The lymph nodes were free. There was pigmentation of the cecal half of the iliac valve. There was no change in the muscle walls.

CASE 4.—Mrs. B., aged 34, had mild mental obsessions and marked depression, with severe congenital constipation. An operation for developmental reconstruction was performed. Tissue examination revealed no pigmentation of the ileum. The cecal half of the ileocecal valve was pigmented. There was pigmentation of the mucosa of the cecum and the hind-gut. Solitary follicles were pigment free. There was no change in the muscle walls. The lymph nodes of the mesocolon were pigment free.

CASE 5.—Mrs. R., aged 55, had chronic constipation for twenty years. An operation for developmental reconstruction was performed. Tissue examination revealed pigmentation of the mucosa only. There was no change in the muscle walls.

CASE 6.—Mr. A., aged 60, had profound toxemia. Obstipation had existed for twenty years. An operation for developmental reconstruction was performed. Tissue examination revealed pigmentation of the terminal portion of the ileum and the entire hind-gut. Pigment involved the solitary follicles as well as the mucosa, extended into the submucosa, and was to be found in the lymph nodes of the mesocolon. There was marked atrophy of the muscle walls.

SERVICE OF DR. BAINBRIDGE

CASE 7.—Mr. M., aged 36, was always constipated. Colectomy was performed. Tissue examination revealed the ileum pigment free. Pigment was confined to the mucosa of the cecum and hind-gut. There was some atrophy of the muscle walls. As an interesting side light on the toxicity of cecal contents in these cases a cubic centimeter of such, from this case, was injected into the peritoneal cavity of a 250 gm. guinea-pig and caused his death in two hours, the symptoms being those of profound toxemia.

SERVICE OF DR. MEEKER

CASE 8.—Mrs. W., aged 42, was troubled with prolonged constipation, etc. Colectomy was performed. Tissue examination revealed profuse pigmentation of the mucosa of the terminal portion of the ileum; also pigment in the solitary follicles and the submucosa.

Three other pigmented intestines are not mentioned in this group because of insufficient clinical data. Of the twelve intestines examined after operation for chronic intestinal stasis, eleven were pigmented. Not including appendixes, we have examined 206 intestinal tissues in our laboratory in the past five years. The foregoing eleven were the only pigmented ones which came to our notice.

COMMENT

It would appear that pigmentation of the hind-gut is a condition dependent on chronic intestinal stasis rather than incident to it. That it is a result, and not a primary contributing cause of obstipation, is indicated by consideration of clinical data in conjunction with histologic findings in tissue obtained both at necropsy and from the operating table. The influence of pigment, after formation, on the normal physiologic function of the hind-gut is, as are most phases

of this problem, a matter on which one is compelled to theorize because of inability to establish facts. Physiology of the hind-gut does not brilliantly illumine the pages of standard textbooks. Other than that the hind-gut serves as a connecting link between the small intestine and rectum and that it absorbs to a certain extent, and secretes a watery enzyme-free fluid, there is but little information pertaining to its functions. That both absorptive and secretory functions should bear directly on the degree of obstipation is understood when one takes into consideration their influence on consistency of fecal mass, lubrication of the intestinal mucosa, and effect on bacterial action. It is, of course, impossible to more than conjecture how materially normal functions of the mucosa are retarded by the presence of pigment. A study, however, of the position of many of the pigment cells would indicate that their interference must be a considerable one. So characteristic was the position of the majority of the cells to Solger, that, noting how they followed the peripheral line of vessels, he attributed pigmentation to circulatory disturbances.

If one recalls for a moment the normal histology of the mucosa of the cecum and hind-gut, he will remember that it is roughly as follows: (a) a single layer of columnar epithelial cells resting on a basement membrane; (b) connective tissue stroma containing central arteries, veins, lymphatic stem and nerves, with fine branches spreading from the central vessels and anastomosing directly beneath the basement membrane; (c) muscularis mucosa composed of a thin layer of muscle fibers separating the mucosa from the submucosa. With this histologic picture in mind, it must be conceded that a foreign substance in greater or less abundance when interposed between anastomosing branches of terminal blood vessels and between or in lymph spaces, mechanically at least, interferes with the normal performance of the functions of these parts.

If secretions are diminished there is a coincident loss of moisture to the fecal mass and defective lubrication of the mucous membrane. This has been graphically described by Lynch in his protoscopic picture of a dry mucous membrane covered with sticky fecal masses. If absorption is retarded, fats which would otherwise pass through the intestinal wall remain within the cavity and both promote and accelerate bacterial decomposition. On the other hand, however, with retarded absorption, there would be less fluid withdrawn from the fecal mass, though this might be a feature of small importance, owing to the turbidity of the fecal current and the consequent extended period during which absorption can take place.

In both the pigmented and nonpigmented cecum and adjacent hind-gut, during chronic intestinal stasis, there appears first to occur a congestion and edema of the mucosa, accompanied by congestion manifest in all blood vessels throughout the several intestinal walls. Following this phase, if the condition persists, there occurs a very slow but progressive atrophy not only of the mucosa but of all walls of the intestine. (By this I do not wish to convey the impression that atrophy continues until fibrous tissue ultimately replaces the normal structures. In no tissue which I have studied was there an absence of any of the normal coats of the intestinal wall, even though they had been extensively thinned out.) Not considering senile atrophy, we may presume these changes to be due,

first, to an irritation of the mucosa which may be either chemical or mechanical and is probably both. After the preliminary irritation, there begins a gradual overdistention followed by loss of tonicity through constant stretching, and disturbance of circulation from pressure of gut content and compression by gut walls. It is more logical to attribute such changes to the causes mentioned than to suppose them to be due to the presence of pigment in the mucosa, though the possibility of a toxic element derived from pigment is within the bounds of speculation.

CONCLUSIONS

If the foregoing premises are correct, it is possible to draw the following conclusions:

1. In true melanosis of the hind-gut, the pigment is not derived from blood pigment, but is a substance between true melanin and fat pigment.
2. This pigment is probably formed by an enzyme which, manufactured by the intestinal contents, acts on the intercellular substance of the stroma of the intestinal mucosa.
3. Pigment-containing cells are derived from plasma cells of the stroma of the intestinal mucosa.
4. Intestinal pigment is primarily an accompaniment and not a cause of chronic obstipation.
5. The clinical significance of intestinal pigmentation concerns the duration and intensity of obstipation, and, while a contributing influence in established obstipation, is not an initial etiologic factor.

ABSTRACT OF DISCUSSION

DR. R. A. LAMBERT, New York: By what method of examination did Dr. Lynch note the disappearance of the pigment in the three cases which he studied?

DR. ALFRED F. HESS, New York: Does the pigmentation occur in children, or only in adults?

DR. JAMES EWING, New York: I have encountered pigmentation of the large intestine somewhat frequently and I think that small amounts of this condition are not so uncommon as Dr. McFarland's references to the literature would indicate. I recall one rather pronounced case in a physician who suffered from chronic anemia and long continued obstipation. The entire large intestine was dark brown. He also suffered from a peculiar degeneration of the voluntary muscle system and of the peripheral nervous system, the exact designation of which puzzled our New York neurologists. We interpreted the intestinal condition as the result of the chronic intestinal obstipation and intoxication.

DR. JOHN W. DRAPER, New York: I had the pleasure, in connection with Dr. Lynch, of furnishing a part of the tissues from which these studies were made. I know nothing of the origin of the pigment excepting what I have learned from the study of Dr. McFarland's paper. We have observed clinically one important matter—the improvement in the cases operated on has in a general way been proportionate to the amount of pigment present. It may be, therefore, that the presence of the pigment, which in most cases was easily discoverable when the abdomen was opened, may be an index of value for the operating surgeon.

DR. JEROME M. LYNCH, New York: I have been studying this question for five years and am sorry that I can throw but little light on the origin of bowel pigmentation. I have seen a comparatively large number of patients. They are all very toxic, constipated, bleed from the bowel occasionally and have severe periodic headaches. The toxicity is relieved if the bowels are kept open, and the pigment gradually disappears if irrigations are continued over a long period. The pigment varies from an ochre to a black shade and is sometimes divided into rectangular blocks. It is an interesting problem, and I hope that this paper may lead to further study and information on this important subject.

DR. W. LANDRUM MCFARLAND, New York: The observations of Dr. Lynch in regard to the disappearance of the pigment were made with the proctoscope. He saw the discolorization of the intestine—the usual picture before the treatment, and the disappearance as the patients were treated—just as you would the fading out of anything that is decolorized. Of course his observations were macroscopic. The youngest case that I have seen on record was that of a person 16 years of age. The worst pigmentations were in persons over 40. The remarks of Dr. Ewing were interesting. The Germans think the condition rare; the Swedes do not. Eight out of the eleven intestines that were sent to me have shown pigmentation, so I do not consider it a rare condition.

WHEN IS CANCER OPERABLE?*

J. WALTER VAUGHAN, M.D.

DETROIT

During the past ten years, my assistants and I have experimented with many various substances in the hope of throwing some light on a better understanding of the cancer problem.

The work¹ first reported contained a brief case report on the use of vaccines prepared from cancer protein, and later publications² gave reports of various scientific findings as they were encountered during the progress of this study.

Other workers, notably Blumenthal³ and Lünchenbein,⁴ have reported clinical observations which corresponded to those that I had previously reported. From a scientific standpoint, the work of Gruner⁵ agrees with changes I have observed chiefly in advanced malignancy, while of decided corroborative value is the research of Murphy,⁶ showing the effect of spleen destruction on the transplantability of tumors.

Indeed, the literature on the subject of malignancy abounds with isolated observations made by many independent investigators which, when taken collectively, all point toward the verification of the conclusions reached by me from my own investigations.

While these investigations have not added much of decided value to the solution of the cancer problem from the standpoint of ultimate control of the disease, yet they have contributed much toward what I might term its intelligent treatment, and they have given us an exact knowledge as to when operative treatment is indicated, as well as to when such treatment will shorten life rather than prolong it.

Obviously it would occupy too much time to give in detail the mass of experimental work that has been done before the facts, on which the following conclusions are based, were elicited. However, these have

all been published before, and the references to such publications are appended, so I will occupy the time by a simple statement of the facts, together with a brief report of the conclusions that must be deduced from them.

Metchnikoff, in his classical work on phagocytosis, was the first to show that tissue cells when introduced into the animal body were ingested by the type of large mononuclear leukocyte that is formed in the spleen. At this time, owing to the importance of his observations on the rôle of the polymorphonuclear leukocyte in bacterial infections, but little attention was paid to his observations on the large mononuclear cell, and he himself never associated this cell with any protective function in malignancy.

The next work calling attention to this endothelial blood cell of splenic origin, and the first associating it with the protective apparatus against malignancy, was that performed by my assistants and myself.⁷ Altogether we have done over 30,000 differential blood counts and have ascertained that there is invariably an increase in large mononuclear leukocytes following the injection of cancer protein into normal persons or animals.

The percentage of increase is dependent on certain factors, chief among which is the number of body cells with which the protein comes into contact.

Thus a subcutaneous injection is followed by a slight increase, an intravenous injection by a greater increase, and the intraperitoneal method gives a still greater increase.

Another important factor is that the sensitizing dose should not be too large—from 5 to 10 minims of a 0.5 to 1 per cent. solution or suspension of either residue or vaccine is sufficient.

This increase in percentage of large lymphocytes is of short duration, lasting from about four to twenty-four hours. During this time the animal is sensitized to large intravenous doses of the protein; but such sensitization is lost when the increase in large mononuclear cells again recedes.

At the time these observations were first made, I was working under the mistaken impression that this reaction was specific for cancer tissue; but the work of Fischera⁸ helped to show this to be untrue.

Fischera was experimenting with fetal autolysate in the treatment of malignancy, and had reported decided clinical benefit in some cases. I immediately started blood counts following injections of fetal autolysate, placental residue, and tissue vaccines from every source, and obtained results of decided interest.

Chief among these was the fact that the more the tissues used reverted to the embryologic type, the greater was the increase in large lymphocytes following its injection. This forced me to the conclusion that we were not dealing with a specific ferment but with a general proteolytic ferment produced by the larger mononuclear leukocytes which is specific only to a limited degree.

This also explained why residues or vaccines made from some forms of malignant tumors gave but a slight increase in large mononuclear cells after injection, while others gave an increase of from 200 to 300 per cent. A careful study of many tumors in this way indicated that the more the tumor reverted to the

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