A Syndrome of Diagnostic Significance

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DISCUSSION

Seven of our 10 patients were females; Peutz7,19 had 5 cases in males and 2 in females. The patient of Touraine and Couder17,18 was a male. For those with the entire syndrome the sexes were equally distributed. The sex was given for 24 cases of the pigment part of the syndrome as 11 males and 13 females.18 Apparently, then, the same sex distribution holds also for the patients with the pigment picture alone.

A rather wide ethnologic spread is evidenced by its occurrence in persons of American, French-

Table 2. Characteristics of the Pigmentation in Proved Cases of Polyposis.

<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>RELATIVE INTENSITY OF PIGMENT SPOTS</th>
<th>PIGMENTATION ELSEWHERE ON SKIN</th>
<th>COLOR OF HAIR</th>
<th>COLOR OF EYES</th>
<th>AGE AT WHICH PIGMENTATION WAS FIRST NOTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Dark brown</td>
<td>Brown</td>
<td>Early childhood</td>
</tr>
<tr>
<td>2</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Dark brown</td>
<td>Brown</td>
<td>Early childhood</td>
</tr>
<tr>
<td>3</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Dark brown</td>
<td>Brown</td>
<td>Early childhood</td>
</tr>
<tr>
<td>4</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Dark brown</td>
<td>Brown</td>
<td>Early childhood</td>
</tr>
<tr>
<td>5</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Dark brown</td>
<td>Brown</td>
<td>Early childhood</td>
</tr>
<tr>
<td>6</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Black</td>
<td>Dark brown</td>
<td>From infancy</td>
</tr>
<tr>
<td>7</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Black</td>
<td>Dark brown</td>
<td>From infancy</td>
</tr>
<tr>
<td>8</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Black</td>
<td>Dark brown</td>
<td>From infancy</td>
</tr>
<tr>
<td>9</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Black</td>
<td>Dark brown</td>
<td>From infancy</td>
</tr>
<tr>
<td>10</td>
<td>++++ +++++ +++++ ++ ++</td>
<td>0</td>
<td>Black</td>
<td>Dark brown</td>
<td>From infancy</td>
</tr>
</tbody>
</table>

Pigmentation present on sole of left foot.

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anomaly of freckles (ephelides) is common in persons of light complexion with blond, light-brown or red hair and lighter-colored irides.

**Pigmentation**

In each case in which data were available pigmentation had been present from early in childhood to the age of twenty or more, with little or no change over the years and no very striking tendency to fade prior to that time. In Case 6 the mother noted the pigment at birth, and in Case 7 it was noted in a picture taken at the age of three months. Peutz\(^{10}\) observed it in the second year of life. He believes that the mouth pigmentation persists but that some fading of the portion on the face may occur after the age of twenty-five. If white light is reflected to reflection of blue rays and absorption of red rays of the spectrum when white light is reflected from pigment particles in the dermis or corium. The patches on the lips and buccal mucosa varied from 1 mm. in diameter up to 5 mm. or slightly larger. Patches in the mouth were most prominent on the buccal mucosa, occasionally on the gums or hard palate and only rarely on the tongue. Those on the lips were more noticeable on the dental than outer aspect and more numerous on the lower than upper lip (Fig. 1, 2, 5, 6, 7, 9, 11 and 16).

Some of the spots had a somewhat stippled appearance when examined by means of a high-power magnifying glass. This phenomenon was present in all cases when looked for (that is, Case 7, 8, 9 and 10). It is of interest that the histologic study of the lesion revealed the pigment deposit to be distributed in vertical bands through the epidermis.

Biopsy of a typical pigmented spot in Case 6 was studied histologically by Dr. Lloyd W. Ketron,\(^{2}\) who made the following remarks on the sections*:

A biopsy has been taken of a pigmented macule on the hypothenar portion of the right palm. The tissue was fixed in formalin and sections stained with hematoxylin and eosin, polychrom and methylene blue and by Giesma's method. The patient would not permit the removal of adequate tissue to make it possible to perform silver nitrate stains.

Although clinically the pigmentation seems to have a uniform and diffuse distribution, the sections reveal that the changes occur mainly in vertical bands (see Fig. 18). In these segments the following alterations are seen in the various layers: in the stratum corneum there are masses of melanin conforming in size and shape with those of cells in most instances; in the basal layer there are increased number of "clear cells" of Masson and perhaps also of the melanoblasts although none of the stains used demonstrate well the branching processes of these cells. Occasionally, one of the rete cells shows melanin granules, and a few cells in the granular layer have yellowish-brown granules. In the cilia there are a moderate number of chromatophores and occasional extracellular accumulations of melanin. One gains the impression that there is slight proliferation of the fixed tissue cells around the superficial blood vessels, which also appear to be dilated. However, because of regional differences this cannot be said with absolute certainty. These changes are similar pathologically to those seen in lentigines. However, because of the age incidence and anatomic distribution, I should hesitate to place them in that group.

*Published here with Dr. Ketron's permission.

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**Table 3. General Information and Characteristics of the Polyposis.**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Nationality</th>
<th>Family History</th>
<th>Malig-</th>
<th>No. of</th>
<th>Location of Polyves</th>
<th>Polyposis Demonstrated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yr.</td>
<td></td>
<td></td>
<td></td>
<td>nant-</td>
<td>Operations</td>
<td>for in-</td>
<td>of Small Intestine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hare-</td>
<td></td>
<td>gerat-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>io-</td>
<td></td>
<td>ops</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>F</td>
<td>American</td>
<td></td>
<td>yes</td>
<td>3</td>
<td>present</td>
<td>stomach</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>F</td>
<td>French-Italian</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>present</td>
<td>small intestine</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
<td>F</td>
<td>American</td>
<td></td>
<td>yes</td>
<td>5</td>
<td>present</td>
<td>large intestine</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>F</td>
<td>Italian</td>
<td></td>
<td>yes</td>
<td>6</td>
<td>present</td>
<td>at autopsy</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>F</td>
<td>American</td>
<td></td>
<td>yes</td>
<td>7</td>
<td>present</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>M</td>
<td>American (Negro)</td>
<td>yes</td>
<td>yes</td>
<td>8</td>
<td>present</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>F</td>
<td>American</td>
<td></td>
<td>yes</td>
<td>9</td>
<td>present</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>M</td>
<td>American</td>
<td></td>
<td>yes</td>
<td>10</td>
<td>present</td>
<td></td>
</tr>
</tbody>
</table>

*Not specifically searched for.
†Patient living.
The above description is essentially what was noted by Touraine and Couder18 and by Siemens12 in the study of biopsies of pigment spots in their cases. However, the vertical bands of pigment noted in our cases were not mentioned in their reports.

One patient (Case 7) had a few small pigment spots on the mucous membrane inside the nose. None of our cases had melanosis coli as evidenced by negative examination by sigmoidoscopy or inspection of the colonic mucosa in operative or autopsy specimens. However, one of Peutz's patients had pigmentation of the rectal mucosa, first noted at the age of four.

To some degree pigment spots were noticed on the face in nine subjects. There are certain distinctive features. In contrast to the mucosal spots, those on the face are usually quite small (1 mm. in diameter or less) and are round and flat with the surface of the skin. The spots are distributed so as to be most numerous about the mouth, in some cases below the nose, about the eyes and more rarely in a butterfly pattern over the bridge of the nose. In other words they are most numerous near the orifices of the face (that is, the eyes, the nostrils and especially the lips). The spots become progressively more sparse on the forehead, temples, glabella and angles of the jaw and in the front of the ears, or, in other words, in the areas removed from the oral and nasal orifices. The facial spots usually have a darker color than freckles, and are more distinctly outlined with no tendency to coalesce as a rule. Peutz19 has been able to follow one family for thirty years and noted a tendency for the facial spots to fade progressively after the age of twenty-five, although the mucosal spots were found to persist unchanged. Facial spots in our cases varied from minimal (Case 7, Fig. 9), to moderate involvement (Case 2, Fig. 1). None showed the marked involvement noted in the cases of Peutz7,10 (Fig. 14) and Touraine and Couder17,18 (Fig. 16). Apparently, the facial distribution of the pigmented portion of the syndrome is most varied, is not the essential portion, and may be absent or disappear as the person gets older.

When the spots were carefully looked for, each patient showed some pigmented areas on the fingers and in some cases on the toes also. To a lesser degree a few patients had spots on the hands and feet as well. On the hands the pigment spots were most numerous on the fingers, varying from a few to many, involving both the plantar and the dorsal surface. They varied in size from 1 mm. to several millimeters in diameter, and were sometimes round and sometimes irregular in shape. As on the face and mucous membranes they were flat. In color they were light to very dark brown. The spots are particularly well depicted in the left hand of Case 2 (Fig. 2). On clinical inspection they were much more evident than is apparent in the photographs, being obscured by high lights in some pictures.

In no case was any pigment spot elevated, vascular or hairy. In addition an important observation is that no patient showed pigmentation on any part of the body in addition to the areas noted. There was no diffuse skin pigmentation, and no accentuation of pigment in the body folds or about the nipples.

The possibility that the pigment portion of this syndrome represents ephelides (freckles) must be considered. There is much against this idea. Freckles are due to inherited aggregates of melanoblasts in the skin producing sharply demarcated yellowish-brown areas, of varying size, and often zigzag in outline. They are more obvious in spring and summer, appear early in life but not in infancy, never occur on the palms and soles, are prominent on the exposed portion of the body and are most likely to occur in persons of light complexion.

On the face, freckles are most numerous over the nose and cheeks and most sparse near the mouth and nostrils. In other words, the distribution pattern of freckles on the face is the reverse of the pattern we have described. In fact, Siemens12 characterized the spots of the syndrome under consideration as "ephelides inversae" because of this contrast in distribution when compared with ephelides.

The most important point against ephelides is the striking and constant occurrence on the lips and buccal mucosa even when the spots are minimal on the face. During the past few years we have examined the lips and oral mucosa of several dozen heavily freckled persons of both sexes and various age groups from childhood up through the third
decade. One was a boy who had won a “freckle contest.” Although heavily freckled persons may show a few lesions on the lips, in no case did we see pigment spots on the buccal mucosa, hard palate or gums.

Lentigo is essentially a localized macular area of hyperpigmentation containing a normal number of melanoblasts. They are usually multiple, dark brown, of varying size and up to 1 cm. in diameter, occurring on the covered parts of the body as well as on the face and hands and appearing later in life than freckles do. They have no characteristic or fixed pattern of distribution. There is no known hereditary predisposition. Mucous-membrane lesions do not occur. The usually accepted description and definition of lentigo seems to exclude the idea that the pigmented portion of the syndrome falls into this category in spite of the fact that Touraine and Couder refer to them as such.

Chloasma, xeroderma pigmentosa, von Recklinghausen’s disease and melanosis of external origin are readily excluded from consideration.

The pigment of this syndrome is undoubtedly melanin. It may well fit into the group of melanin pigments classified by Becker and Obermayer as “melanosis associated with increased number of melanoblasts.” Its hereditary tendency (See Fig. 10, 12, 13 and 15) is best explained on this basis. Is the pigment syndrome a variant of ephelides or a separate and distinct form of melanosis? The latter possibility appears most likely to us, but we have been unable to prove or disprove this thesis. In essence, the nature of the pigmented anomaly remains obscure. Apparently, it is limited to, or most common in, persons of dark complexion.

A summary of the data concerning the pigmentation is given in Table 2.

**Intestinal Polyposis**

The other portion of the syndrome consists of intestinal polyposis. Apparently, in each case the polyps are distributed throughout the entire intestinal tract with their most striking clinical manifestations in the small intestine.

The features referable to the polyposis in our 10 cases are given in Table 3. The presence and nature of the polyps in each subject were definitely established by means of one or more operations on the small bowel in all cases, and in addition by post-mortem examination in 3 cases.

The symptomatology of these patients was referable chiefly to the small intestine with numerous episodes of abdominal pain and signs of minor obstruction terminating in one or more attacks of small-bowel intussusception. Surgery of the small intestine was performed on these 10 patients, varying from one to four operations each. Several patients had melena of varying degree. In Case 1 a sprue-like syndrome developed after resection of portions of the small intestine; the procedure led to inanition and contributed to her death.

By contrast, rectal and large-bowel symptoms and signs were minimal or absent. One patient (Case 6) had significant trouble with rectal polyps, but this disappeared after the age of four, several local operations for removal of the lesions having been performed.

Just as the symptomatology pointed to the small intestine principally, operation and autopsy revealed the majority of the polyps to be located in the small intestine in all 10 cases. Furthermore, of the small intestine, it was principally the jejunum that was involved. Peutz had a similar experience with polyposis involving predominantly, but not exclusively, the small intestine in his 7 cases. Four of Peutz’s patients had nasal polyposis, and 1 bladder polyposis. Touraine and Couder’s patient was said to have only rectal polyps, but adequate small-bowel studies were apparently not done.

Although predominate in the small intestine, polyposis was also present in the stomach and colon in the 5 autopsied cases in our series. Polyps were demonstrated in the colon of 3 of the living patients and in the stomach of 1. Their presence or absence in the colon and stomach of the other patients was not demonstrated. It appears that the polyposis is present throughout the entire intestinal tract but most prominent in the small intestine.

The intestinal lesions were the usual adenomatous polyps as evidenced by histologic study of resected or autopsy specimens, or both, in all 10 of our cases. This was true also of the cases of Peutz, Foster, and van Dijk and Oudendaal. A representative gross lesion of the small intestine from one of our patients (Case 7) is shown elsewhere. In summary, then, the intestinal polyposis in these patients appears grossly and microscopically similar to generalized intestinal polyposis in persons not having the associated pigmented syndrome.

The well known tendency for multiple polyposis of the colon to develop malignancy apparently holds to some degree for the small-bowel polyps in cases of this syndrome. In 1 patient (Case 3) in this series, 2 of Peutz’s 7 patients and possibly 3 of Foster’s the small-bowel lesion became malignant. The incidence of cancer here is not so great as that in the hereditary large-bowel polyposis but is distinctive enough nevertheless.

Most of the cases of multiple intestinal polyposis described in the literature appear to have been limited to the colon or rectum, or both. Symptomatology in these cases is rectal or colonic. It is quite rare to find any mention at all of lesions in the small intestine in these reports. Since exploratory procedures were commonly performed, any
small-bowel polyps present would probably have been found and comment made about them. Ladd and Gross studied the records of 92 cases of intestinal polyposis at Children's Hospital in Boston. In only 2 of these were polyps noted in the small intestine. At the Mayo Clinic, Coffey in a study of 29 cases of multiple intestinal polyposis, noted their localization to the colon in all but 2, in which the polyps were disseminated throughout the stomach and entire intestinal tract. Apparently, multiple polyps of the small intestine are quite rare as contrasted with multiple polyposis of the large intestine. On the basis of 7000 consecutive autopsies at the Cook County Hospital, Lawrence concluded that polyps are approximately twelve times more common in the colon than in the small intestine.

In contrast to the numerous papers dealing with polyposis of the colon and rectum is the distinct paucity of studies referable to multiple polyposis of the small intestine, especially cases with a heredofamilial pattern similar to that in colonic polyposis. The recent review by Ravitch on polyposis of the small intestine and polyposis of the entire gastrointestinal tract further confirms the rarity of these two varieties.

Our 10 cases, most of which were heredofamilial, seem a large number in view of the rarity with which such cases are described in the literature. Peutz 7 similar cases makes the number even more impressive. The additional fact that each member of this relatively large group with this unusual intestinal lesion showed a peculiar and distinctive type of pigmentation seems to us to indicate that the association is not fortuitous but of real diagnostic significance.

We have not found any report with adequate bowel studies in which the pigmentation portion of the syndrome was associated solely with large-bowel polyposis. A number of surgeons with extensive experience with large-bowel polyposis, with whom this subject was discussed, were unable to recall a personally recognized example.

Heredit*

It is well established that multiple polyposis of the large intestine is frequently hereditary. Dukes in an exhaustive review of the subject, concludes that it "is an inheritable disease which is transmitted by both males and females, that both males and females suffer from the disease and that the inheritance can be traced through several generations." Gates reviewed the genetic aspects of polyposis of the large intestine and was able to discover the pedigree of a total of forty families in the literature. He concluded that the condition is a simple mendelian dominant with an occasional skip in some families.

As pointed out above, multiple polyposis of the small intestine or of the entire gastrointestinal tract, as seen in the syndrome discussed in this paper, appears to be an entity distinct from the more common colonic polyposis; yet our data indicate that it follows a similar genetic pattern. That this type of polyposis is likewise often hereditary there can be little question. Among our 10 cases, two families are represented by 3 cases each. In the literature there are no genealogic charts large enough to permit any conclusion regarding genetics. There are, however, reports of several families in which more than one member suffered from polyposis of the small intestine.

That the pigmentary portion of this syndrome is likewise hereditary is inescapable from the two family groups among our 10 cases, and from the fact that Touraine and Couder in reviewing the literature on the pigmentary anomaly alone, found 31 cases, of which 22 were familial. These authors presented several genealogic charts of the pigmentary anomaly indicating inheritance as a simple mendelian dominant.

Our genealogic tables of the Dutch family (Fig. 13), the Welsh family (Fig. 15), the Boston family (Fig. 12) and the Harrisburg family (Fig. 10) not only offer proof of the hereditary nature of the complete syndrome but also permit certain other conclusions.

In the first place the syndrome appears to be inherited as a simple mendelian dominant. The involvement rate of approximately 50 per cent in the second and third generations of the Dutch family, and in the second generation of the Harrisburg family, is consistent with, although not absolute proof of, such an inheritance through the mating of persons heterozygotic for this characteristic with persons not carrying this trait. In favor of inheritance of the syndrome as a dominant is the fact that, although rare, it occurs in a large percentage of members of tainted families.

Secondly, from these four charts, the characteristics constituting the syndrome appear to have a high degree of penetrance, occurring probably in the majority of those who carry the necessary factors.

Thirdly, there are no generation skips. Both males and females carry the factor, and both are affected about equally.

Further study of the genealogic tables (Fig. 12 and 13) impresses one with the fact that whenever patients were actually examined and subjected to complete studies, the full syndrome, polyposis and spots, occurred together in the same person. "Gene linkage" (that is, the presence on the same chromosome of a separate gene for each characteristic) will not explain the association. Snyder states it thus:

*We are indebted to Dr. Bentley Glass, of the Department of Biology, Johns Hopkins University, for his assistance in the preparation of this portion of the manuscript.
The occurrence of genetic linkage between the genes for two traits does not change the association for these traits in the population from what it would be if they were not linked. Stated inversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes for these traits.

The correct explanation for this syndrome as for the majority of the other hereditary syndromes must be the presence of a single pleiotropic gene responsible for both characteristics, the polyyps and the spots.47

We still await the autopsy report of a patient with the characteristic pigmentation that shows absolutely no polyps of the intestine on careful search. That the converse situation occurs seems probable. There may be several reasons for the occurrence of generalized intestinal polyposis or of polyps of the small intestine without spots. First, it must be appreciated that clinical identity does not necessarily mean genetic identity; 2 cases of polyposis clinically identical may have quite different genetic backgrounds. Secondly, in other inherited syndromes, such as Marfan's arachnodactyly, essential familial xanthomatosis and von Recklinghausen's disease, there may be in the same family great variability in the completeness or degree of expression of the individual characteristics, because of factors not well understood. That variability may, at times, be present in this syndrome, although we have no definite evidence of it. It might be subsequently demonstrated that in the same family some members show only polyposis, and some only spots.

Summary

On the basis of 10 cases studied, an attempt is made to establish a syndrome that previously was not clearly identified in the English medical literature and recognized to only a very limited extent elsewhere. By supplementing our own cases with those discovered in a search of the literature and with data from personal communications, it has been possible to assemble a total of 22 proved, 5 probable and 4 possible cases.

This syndrome consists of two features: distinctive melanin spots of the buccal mucosa and lips — the face and digits may be involved to a variable extent, but the mouth pigmentation is the sine qua non of this portion of the syndrome; and polyposis (synonyms are adenomatosis and papillomatosis) of the small intestine. The stomach, colon and rectum may be involved, but the presence of polyps in the small intestine is the constant feature of this portion of the syndrome.

Our group of 10 cases included 6 in which more than one member of the same family was involved. Sufficient genealogic data are reported to demonstrate the hereditary nature of the syndrome, which appears to be inherited as a simple mendelian dominant. Sporadic cases also occur.

The syndrome appears to have important diagnostic significance in that the external manifestations may be of considerable value in the recognition of the intestinal condition.

As a result of several lectures on this subject, 3 additional cases have been called to our attention since the preparation of the manuscript. Two were examined in detail by one of us — 1 through the courtesy of Dr. C. Stuart Welch of the Joseph H. Pratt Diagnostic Hospital, Boston, and the other through the courtesy of the staff of the United States Naval Hospital, N.N.M.C., Bethesda, Maryland. (A colored illustration of the latter case was reproduced with the first section of this report.) All 3 patients had small-bowel polyposis, one or more operations for intussusception of the small intestine and the typically distinctive melanin spots. The last 2 cases will be reported separately by the institutions mentioned above. These additional cases provide further evidence that the syndrome is a distinct entity.

References

25. Kottron, W. L. Personal communication.