THE PEUTZ SYNDROME: REPORT OF AN AFFECTED FAMILY

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In 1921, Peutz[1] described the syndrome of muco-cutaneous pigmentation and gastro-intestinal polyposis inherited through a Mendelian-dominant gene. An earlier report by Sir Jonathan Hutchinson[2] in 1896 of a similar disease in identical twins is probably an example of the same condition, although Peutz is generally credited with the first clear description of the syndrome. In 1949 Jeghers *et al.*[3] reviewed the literature, described the syndrome more fully, and added 10 cases of their own. Dormandy[4] has since published an authoritative review of the subject, adding 21 cases of his own. To date, we have been able to trace a total of 102 cases in the literature, including 14 affected families. Probably many cases are missed.

The following report of a family exhibiting the condition is presented:

CASE REPORTS

Case 1

First Admission. Miss E.E., aged 18, was admitted to the Johannesburg General Hospital on 17 August 1957 complaining of peri-umbilical abdominal colic for 32 hours. It was associated with vomiting and one day's constipation. Two months before admission she had experienced similar colic, which had disappeared after 2-3 hours. Except for the usual childhood illnesses, she had been quite well all her life.

On examination, she was seen to have a freckled face, which was not regarded as abnormal at the time. Her abdomen was soft and non-tender but showed slight fullness in the lower half. After 12 hours' observation, her abdomen became tender and a definite mass was palpable in the right iliac fossa. A laparotomy was then decided upon.

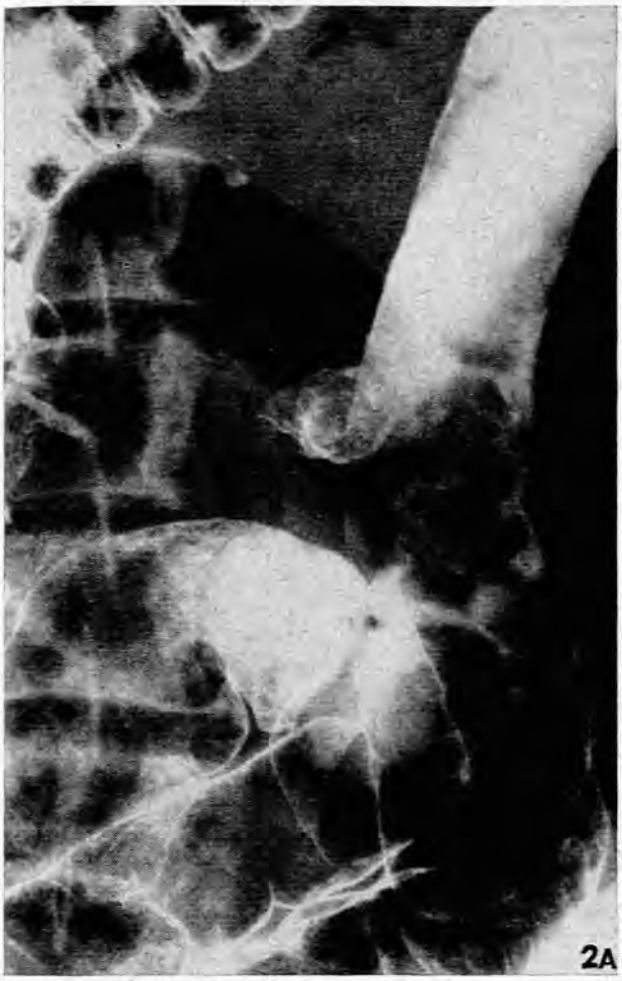
At operation an irreducible ileo-ileal intussusception was found 30 cm. from the ileo-caecal valve. Resection with end-to-end anastomosis was performed. A further search for polypi was not made at the time because the Peutz syndrome was overlooked and because it was considered that the intussusception had probably been caused by a Meckel's diverticulum in view of its site. The patient made an uneventful recovery.

Fig. 1. Diagrammatic illustration of the intussusception in cases 1 and 3 to indicate the situation of the polyp some distance proximal to the apex of the intussusceptum.

On section, the specimen showed a compound intussusception caused by a polyp which, surprisingly, was not at the apex of the intussusception (Fig. 1).

Second Admission. Miss E.E. was readmitted on 24 December 1957, complaining of abdominal colic and vomiting.

Our attention having in the meantime been directed



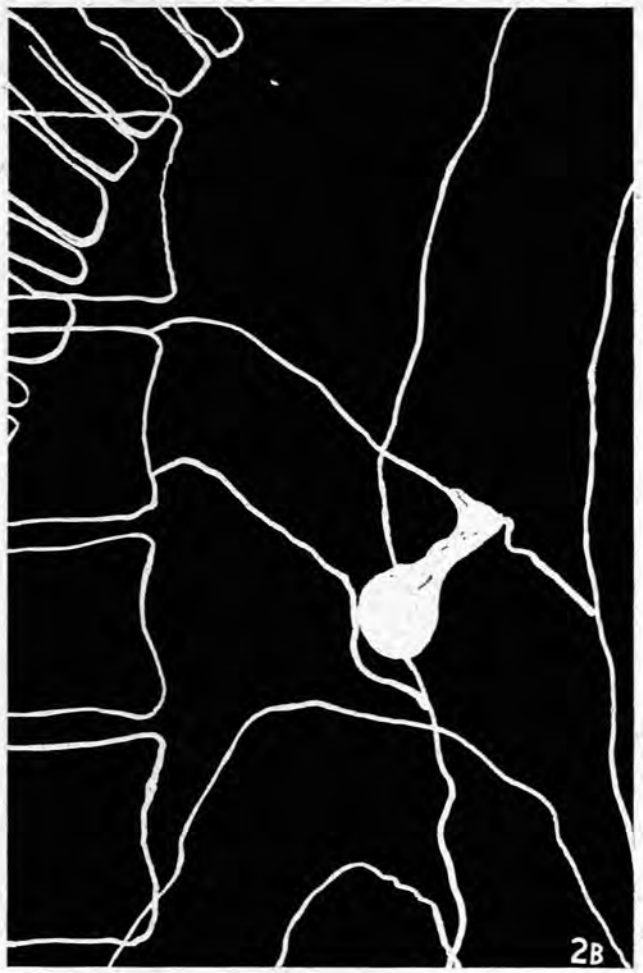


Fig. 2. Contrast barium enema (A), with diagrammatic representation (B), showing the polyp in the terminal ileum in case 2.

to the Peutz syndrome, we noticed that the patient had, in addition to the circumoral freckling, the classical melanin pigmentation of the lips and buccal mucosa. The abdomen was slightly distended but soft and non-tender and a diagnosis was made of sub-acute intestinal obstruction due either to further intussusception or adhesions from the previous operation. Signs and symptoms disappeared on gastric suction and intravenous fluids and she was discharged on the 4th day.

She has had no recurrence of the symptoms to date and barium series have revealed no further polypi.

In view of our findings it was decided to investigate the patient's family and it was found that a younger sister and the mother also had facial freckling and the classical mucosal pigmentation, although the mother's pigmentation had almost completely faded. The father and an elder sister had no pigmentation and they were not subjected to barium series at the time. The elder sister, however, was admitted to the gynaecological ward of the Johannesburg General Hospital in February 1958 complaining of pain in the left iliac fossa. Barium enema revealed no abnormality and she recovered without a definite diagnosis being made.

The family stated that the maternal grandmother, now dead, had similar pigmentation but as far as they knew had never suffered from gastro-intestinal disturbances.

Case 2

The younger sister of case 1, Miss C.E., aged 15, on barium meal and enema showed the presence of polypi in the terminal ileum and caecum (Fig. 2). She exhibited the classical buccal pigmentation (Fig. 3) and also gave a history of having had a rectal polyp removed as a young child. She had had no symptoms. At laparotomy on 12 March 1958 2 polypi were noted in the caecum, one in the ileum 30 cm. from the ileo-caecal valve, and one in the jejunum 30 cm. from the duodeno-jejunal flexure. The caecal polyps were removed through a caecotomy incision, while the ileal and jejunal polyps were removed by resection of about 10 cm. of bowel with end-to-end anastomosis in each case. An appendicectomy was also performed. The patient recovered uneventfully from this operation and sigmoidoscopy was performed on 22 March 1958. A polyp, 4 cm. from the ano-rectal junction, was removed and the rest of the rectum noted to be normal up to 18 cm.

The pathological report on these polypi (Dr. M. D. E. Manson) was as follows: 'Sections of these specimens show the characteristic features of benign adenomatous polypi. No evidence of malignant neoplasia has been observed in any specimen. Sections of the appendix show the presence of lymphoid hyperplasia and there is fibrosis of the peritoneum of the distal third. In addition, a small sessile polyp has been identified in the mucosa close to the tip'.

Case 3

The mother of case 1 and case 2, Mrs. A.M.E., aged 50, showed no abnormality on barium meal or enema and had had no symp-

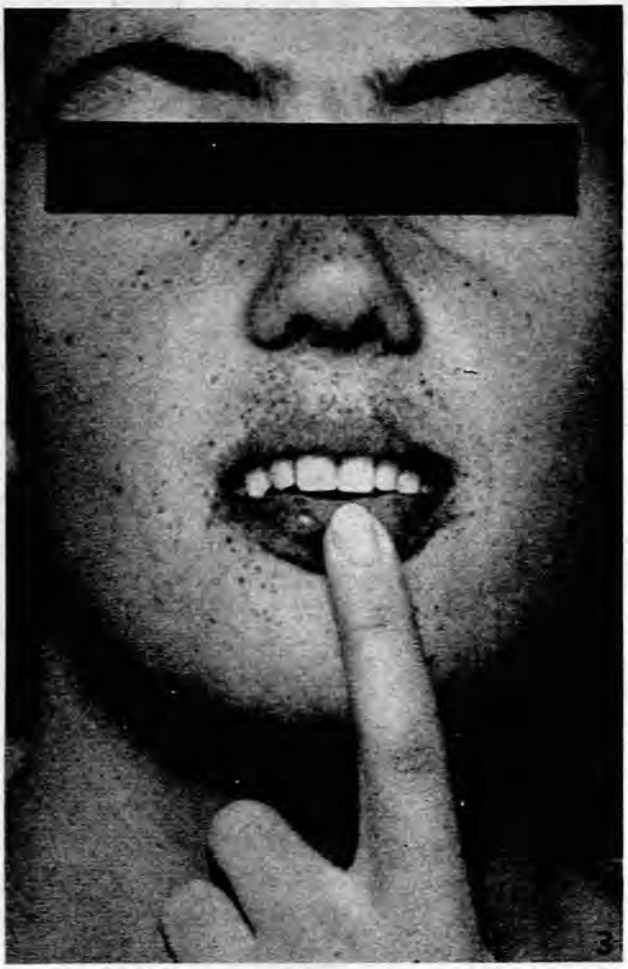


Fig. 3. Photograph of case 2 showing the buccal pigmentation.

toms up to this time. She stated that her pigmentation had faded appreciably over the years. She was admitted with a history of melaena and abdominal pain for 1 day.

A large, non-tender, round, mobile mass was palpable in the lower abdomen, and the patient was subjected to laparotomy on 6 May 1958. At operation, an irreducible intussusception at approximately the jejuno-ileal junction was resected. Further search for polypi revealed one in the jejunum proximal to the intussusception, 3 in the terminal ileum, one in the colon at the splenic flexure and 2 at the recto-sigmoid junction. These were all sessile and removed through multiple enterotomies.

The patient made a good recovery delayed slightly by mild wound sepsis. Histological section of the polypi from both the large and small bowel showed them to be simple. No evidence of malignant neoplasia was observed. The intussusception was compound, as in case 1, with the polyp situated some distance from the apex.

DISCUSSION

1. *Heredity*

The 102 cases of Peutz syndrome we have found reported in the literature include 14 families manifesting the disease. Our family is illustrated genetically in Fig. 4. This conforms to the previously reported patterns of transmission and it is probable that, although all the sufferers in this family were females, the disease is inherited as a Mendelian dominant which is not sex-linked.[3] Sporadic cases may possibly result from gene mutation.

2. *Pigmentation*

Our cases exhibited the classical melanin pigmentation on and around the lips and on the buccal mucosa. No pigmentation was noted on the palate, gums, extremities or other sites reported by other authors.[3, 5] In the two daughters there were, in addition, numerous light-brown freckles on the face. All three patients were fair-skinned, in contradistinction to the dark complexion of most reported cases. The pigmentation in the mother was barely discernible as it had faded over the years. This agrees with Peutz's observation[1] concerning the disappearance of the pigmentation with advancing years.

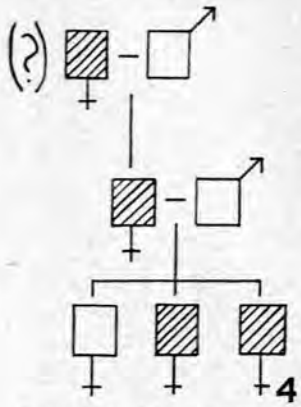


Fig. 4. The shaded squares represent members of the family manifesting the Peutz syndrome. There is no conclusive proof that the maternal grandmother suffered from the disease.

3. *Distribution of Polypi*

Cases 2 and 3 showed widespread distribution of polypi in the small and large bowel. An essential part of the syndrome is the presence of polypi in the small bowel, but over half the reported cases showed polypi in the large bowel as well. Polypi have been found in the stomach[3, 6] and case 2 showed a polyp in the vermiform appendix.

A distinction must be made between this syndrome and familial polyposis coli. where polypi are not found in the small bowel and there is no oral pigmentation.

4. *Presentation*

Intussusception is the classical complication of the condition (cases 1 and 3) and may be progressive (as in our cases) or transient. Case 1 gave a history of one previous attack of colic but many reported cases give histories of intermittent colic and the presence of transient tender 'lumps' in the abdomen extending back over many years. The clinician may notice these lumps on abdominal examination and be surprised to find they have disappeared in hours or even minutes.

The syndrome may also present with diarrhoea, intestinal bleeding or prolapsed rectal polyp, or, to the dermatologist, as oral pigmentation.

5. *Radiology*

In all cases showing the typical pigmentation meticulous radiological investigation should be made of the stomach and the small and large bowel.

In the stomach, polypi are best demonstrated by prone and supine barium mucosal studies, when they are seen as rounded filling defects disturbing the normal rugal pattern. Gastric polypi are not infrequently found in barium-meal examinations and, when demonstrated, the remainder of the gastro-intestinal tract should be examined with a high index of suspicion.

The duodenum is readily examined by the use of a compression cone and serial films. Between the duodeno-jejunal flexure and the caecum, however, polypi are notoriously difficult to demonstrate and, for this reason, Bailey[7] believes that radiology may be of little help since, in one of his cases, X-ray examinations were reported as negative although a

pedunculated jejunal polyp was demonstrated at operation. This also occurred in one of our patients (case 3).

A small quantity (4 oz.) of barium cream is administered orally and its progress through the small bowel observed at ½-hourly intervals by films and, if necessary, fluoroscopy. Polyps will be seen as small radiolucent filling defects. Gas bubbles may cause some confusion but, apart from this, the only condition likely to be confused with polyposis is pneumatosis cystoides intestinalis and here the filling defects tend to lie in the bowel wall rather than in the lumen and show on plain films as multiple translucencies.

Intussusception may be precipitated by barium meal[5, 8] and we devised a special technique of investigation for patients with a history suggesting recurrent obstruction. A water-soluble, opaque medium (urografin 76%) was used and 60 c.c. of it was administered through a naso-gastric tube with the tip lying within the duodenum. The small bowel was then gently insufflated with air and the progress of the medium plus air observed under the screen at short intervals and films taken approximately every 15 minutes. This method was used in case 2, producing a superb double-contrast demonstration of small-bowel detail, but no polypi. We intend to use carbon-dioxide for future insufflation.

During a phase of intussusception, one may, on horizontal-ray films, see dilated loops of small bowel with fluid levels due to small-bowel obstructions. The demonstration of a 'beak'[9] gas shadow may enable one to diagnose intussusception on plain films.

In large-bowel examination, the most important single factor is the meticulous preparation and cleansing of the bowel to avoid the presence of faecal matter. Thereafter the method of examination used varies in different centres. The method we employ is the double-contrast barium enema. After evacuation by the patient of most of the barium suspension used for the normal enema examination, the bowel is insufflated with carbon dioxide[10] or nitrous oxide gas, and the polypi are shown either as single filling defects or pedunculated masses projecting into the bowel lumen (Fig. 2). Where preparation has been adequate polyps of 0·5 cm. and more should be demonstrable. Gas and barium will usually outline the terminal part of the ileum and enable polypi to be demonstrated there. The use of soluble gases for insufflation is preferred to air because the danger of gas embolism is less and the patient suffers less discomfort as the gas is rapidly absorbed. Differentiation of faecal material from polypi forms the chief problem in colonic examination, but gas bubbles and oil globules remaining from oily aperient administration may cause difficulty as well.

Gianturco[11] and Wietersen[12] are enthusiastic about the high-kilovoltage single-contrast method of demonstrating large-bowel polypi, but so far we have had little experience of this technique.

6. *Pathology*

The polypi in the Peutz syndrome are adenomata. They may be sessile or pedunculated. They seem to be capable of eruption at different ages. The naked-eye growths do not appear synchronously[4] and normal-looking gut may separate polyp-bearing segments. Many years may elapse between the appearance of new crops of polypi and they may even regress spontaneously, particularly in the colon,[13] or break off and be evacuated.

Bailey[7] has analysed 67 reported cases in which there was adequate histological knowledge of the polypi and found that malignant change had occurred in 24%. The polypi were situated in the small intestine in 19% of the 67 cases. Dormandy,[14] however, casts doubt on the pre-malignant nature of these tumours, at least in the small bowel. He states, 'Histologically many show the classical features of an early well-differentiated adenocarcinoma, especially apparent invasion of the submucosa and muscularis, but the clinical follow-up always casts doubt on the pathological diagnosis.' We can, in fact, find no recorded cases where the patients diagnosed as having adenocarcinomata actually died as a direct result of them. Dormandy[15] also states, 'I think that the origin of many small intestinal polyps from the deeper layers of the bowel wall accounts for most histological diagnoses of malignancy. Examining serial sections of 2 operation and post-mortem specimens of small bowel I found a number of areas of microscopic intramural adenomatosis in parts of the gut which looked normal or almost normal to the naked eye. These microscopic adenomas vary in complexity from simple "vesicles" to more substantial nodules; they tend to be grouped together (often around one or two naked-eye polyps); they interrupt the continuity of the muscle coat; and may show some degree of cellular irregularity (or immaturity) and great mitotic activity. The apparent "invasion" of the deeper layers of the bowel wall by large naked-eye polyps would seem to reflect their origin rather than an ominous late development in their natural history.'

No proof, other than Bailey's reference,[7] can be found of the malignant potential of the large-bowel adenomata. One might presume, however, that these, in contradistinction to the small-bowel adenomata, harbour the accepted capability of all large bowel polypi to undergo eventual malignant change as in familial polyposis coli.[16] One can, however, only surmise on this point.

The intussusceptions in cases 1 and 3 were both compound and the polypi were not found at the apex of the intussusception. This compares well with Wardill's observations,[17] in which he showed that mere traction upon the polyp by intestinal movements does not account for the formation of the intussusception. He postulated that the tumour acts as a foreign body and produces spasmodic contraction of the gut around it, with inhibition of the part immediately distal. Peristalsis then invaginates the proximal into the distal bowel slightly ahead of the polyp, which is carried onwards though not at the apex of the intussusception.

Intussusception may occur in polyposis without a naked-eye polyp appearing in the intussusception. Dormandy[15] surmises that areas of micro-adenomatosis possibly interfered with normal peristalsis and initiated abnormal waves of contraction.

7. *Treatment*

Operation is indicated in the presence of complications such as excessive bleeding or intussusception, although many intussusceptions obviously resolve spontaneously. A problem arises when a case is proved to be one of polyposis on barium series without symptoms or when symptoms occur intermittently. Many authors advocate prophylactic clearance of small-bowel polypi in the Peutz syndrome.[5, 7, 18, 19] The points in favour of clearance are:

(*a*) These patients may die from the effects of multiple intussusceptions or anaemia.

(*b*) It is thought by some[7] that these tumours are pre-

malignant. This is probably an untenable argument in the light of Dormandy's observations[14, 15] and may therefore be discounted.

The points against clearance are:

(*a*) The distribution of the polypi may be too extensive to allow of adequate removal while leaving behind enough bowel for adequate physiological function.

(*b*) These tumours grow sporadically at various ages and removal of one crop does not guarantee that a further growth in another section of the bowel will not occur.

(*c*) These tumours are not all visible to the naked eye and many are likely to be left behind at operation.

A prophylactic clearance was attempted in case 2 because our interpretation of the available literature at the time seemed to suggest that these small-bowel polypi were pre-malignant. In the light of our further reading[4] it was probably an inadvisable procedure.

When these adenomata occur in the large bowel, however, the outlook is somewhat different. Although there is no incontrovertible evidence to show that they are pre-malignant when situated in the large bowel as in familial polyposis coli, it is probably safer to excise them. Total colectomy seems a most radical procedure to undertake when the hazards of leaving these tumours alone is not established and we venture to suggest that local resection or excision with careful post-operative follow-up is probably the procedure of choice.

SUMMARY

A report is presented of 3 members of a family manifesting the Peutz syndrome.

The salient features of the syndrome are discussed, with particular reference to the pathology, clinical presentation, radiological investigation, and treatment.

We wish to thank Dr. K. F. Mills, Medical Superintendent, Johannesburg General Hospital, for permission to publish these cases, Mr. J. A. Douglas, under whose care cases 1 and 2 were admitted, Mr. S. Skapinker, who performed the operation on case 3, and Prof. D. J. du Plessis for his helpful advice in the preparation of this paper.

ADDENDUM

Since the completion of this article a report of a case of the Peutz syndrome which developed a proved adenocarcinoma in a polyp-bearing area of small bowel has appeared in the literature.[20] We believe this does not invalidate the views expressed concerning the pathology and treatment of the condition but serves to illustrate the extreme rarity of malignant change in the small bowel adenomata.

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