The study of sudden amnesia indicates that it is not possible to draw any sharp dividing-line between organic and functional disabilities and that it is not always possible to distinguish clinically the causes of pathological forgetting.

Summary

The aetiology of sudden loss of memory has been investigated in two series of cases, totalling 74 patients who were submitted to a full neurological and psychiatric examination.

In both series a large proportion suffered from undetected gross organic nervous disease. In the majority, whether organic disease was present or not, a simple psychogenic cause was found and the amnesia could be demonstrated to be a psychological escape mechanism. There is evidence that organic nervous disease may predispose to this type of psychological mechanism. Sudden amnesia is a temporary state that responds well to simple psychotherapy, which can be given, if necessary, in a casualty department. It is essential in such cases to seek the causes of the patient's underlying maladjustment not only in his life and circumstances but in his central nervous system as well.

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An urgent appeal to governments, scientists, and industry to intensify research into the global problem of insect resistance has been made by the Technical Conference on Insect Resistance called together by the World Health Organization in Geneva recently. According to a statement issued by W.H.O., in 1946 only two kinds of insects of public health importance, the house-fly and certain kinds of mosquitoes, were resistant to D.D.T. To-day they number 38, among them several species of malaria-transmitting mosquitoes, plague-carrying fleas, and typhus-bearing lice. Countries all over the world have spent huge sums of money to control the great insect-borne pestilences. Faced with the possibility of failure, they have no practical solution for the control of resistant insects except emergency switching from one insecticide to another. But scientists are running out of effective insecticides which are at the same time economic and non-toxic to man, although chemical firms are testing as many as 50,000 compounds a year for their insecticidal properties. The world may soon face an emergency because of the dynamic nature of the resistance problem as opposed to the more static nature of many other scientific and technical problems.

POLYPOSIS OF GASTRO-INTESTINAL TRACT: THE PEUTZ SYNDROME

BY

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The association of multiple adenomata of the gastro-intestinal tract with melanin pigmentation of the oral mucosa, lips, and face was first described by Peutz (1921), but his description attracted little attention at the time. The subject was fully reviewed by Jeghers *et al.* (1949), and since then many cases have been reported. The syndrome is, however, still not widely known, and the significance of the characteristic melanin pigmentation may not be recognized even if it is noted on clinical examination, and experience has shown that it may be missed altogether if not especially sought.

In this paper four cases of gastro-intestinal polyposis are described, in two of which oral and facial pigmentation was certainly present, but it was not noted in the other two. My purpose is, firstly, to draw attention again to this important association, which may prove a useful diagnostic aid, and, secondly, to show that there is without doubt a considerable risk of malignant change developing in these polyps and to discuss the problems of treatment posed by this tendency.

Case 1

A woman aged 35 who had suffered from recurrent attacks of abdominal pain for 17 months was admitted to University College Hospital in June, 1955. The pain was ill localized, but appeared to begin in the epigastrium. The attacks lasted one to four hours and occurred at intervals varying from a few days to five or six weeks. The pain, which was intermittent, with intervals of complete freedom between the spasms, had been more severe recently. During the attacks, which were not related to food, she felt sick but did not vomit. Usually diarrhoea followed subsidence of the pain, and on several occasions she had passed a little fresh blood in the stool. She also suffered from mitral stenosis and atrial fibrillation, and the first attack of pain occurred about six weeks after a successful mitral valvulotomy had been carried out at another hospital.

She had no children and no brothers or sisters. She could not recall that her parents (now dead) had ever suffered from any serious abdominal symptoms.

On examination she was seen to be a thin, healthy-looking woman. Atrial fibrillation at 72 a minute was controlled with digoxin. A tender, mobile, soft sausage-shaped mass was felt in the left iliac fossa. Rectal examination was negative. Sigmoidoscopy showed no abnormality. There was melanin pigmentation of the face, lips, hands, and feet, consisting of numerous dark-brown and black discrete macules, which were particularly numerous on the lower lip, around the medial side of the eyes, on the back of the hands and fingers, and on the dorsum of the feet. Scattered over the face were several other lighter-coloured spots resembling freckles. Mucosal pigmentation was present on the buccal surface of the lips and cheeks, consisting of several dark blue-black patches varying from 1 to 5 mm. in diameter. (N.B.: this pigmentation was not recognized at the early examinations, being noted only later when it was specially looked for.)

X-ray Examinations.—Barium-meal and follow-through examination carried out elsewhere shortly after the first attack of pain showed the signs of an entero-enteric intussusception of the upper jejunum. Three subsequent barium follow-through examinations were carried out: the first two

of these showed no abnormality apart from some "hold-up" in the upper jejunum; the third demonstrated a pedunculated polyp in the jejunum. Barium enema was negative.

Operation.—At laparotomy on June 29 several small entero-enteric intussusceptions were discovered. These were easily reduced, and in relation to them many polyps were palpated in the jejunum and ileum. The greatest concentration of these was in the ileum, about 3–4 ft. (90–120 cm.) above its termination. Twelve of the larger polyps were removed by enterotomy, and a 10-in. (25-cm.) length of ileum, containing a large number of polyps, was resected, continuity being restored by end-to-end anastomosis.

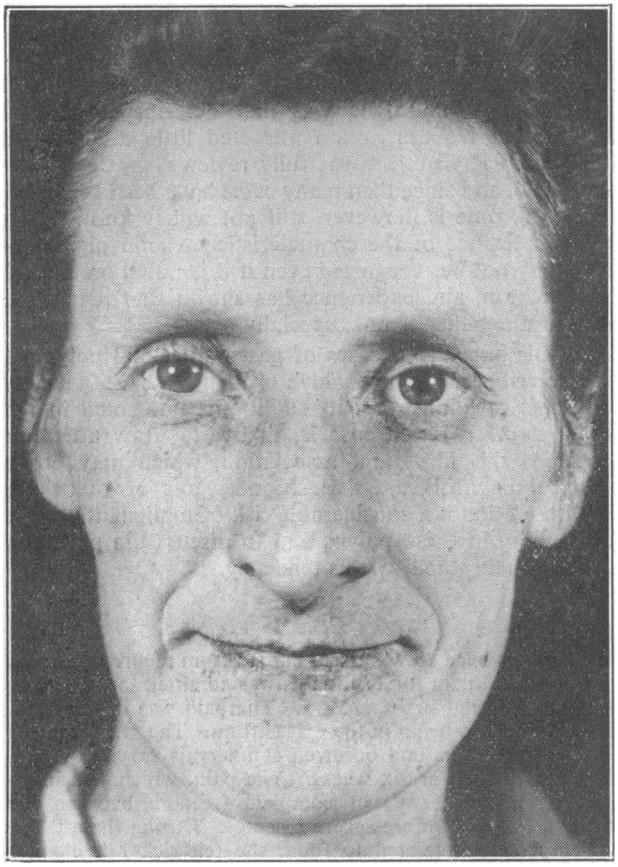

FIG. 1.—Pigmentation of lips and face in Case 1.

Pathology.—The twelve separate polyps were found on microscopy to be benign adenomata, and the 10-in. (25-cm.) length of ileum was studded with polyps. Thirteen of the latter were comparatively large, and on microscopy were also found to be benign adenomata; there were numerous smaller polyps and sessile tumours which were not sectioned.

Convalescence from the operation was uneventful. The patient has been followed up and seen at three-monthly intervals, remaining symptom-free. On January 1, 1956, sigmoidoscopy revealed a pedunculated rectal polyp, about 1 cm. in diameter, at 12 cm. This was removed with the diathermy snare; microscopy showed a benign adenomatous polyp.

Case 2

A man aged 56 was first seen at Harrow Hospital in December, 1946, when he was admitted as an emergency case with acute intestinal obstruction. He gave a history of several previous attacks of abdominal pain, sometimes associated with the passage of blood in the stools.

First Operation.—In 1937 a polyp had been removed from his rectum at another hospital. On laparotomy an irreducible ilio-ileal intussusception was found which was resected. The specimen was not examined histologically, but it is recorded that the apex of the intussusception was formed by a collection of polypoid tumours.

He was not seen again at Harrow Hospital until 1954, when he attended the out-patient department complaining of recurrent attacks of abdominal pain accompanied by diarrhoea.

On examination a soft mobile mass was felt in the right iliac fossa. Rectal examination was negative. Sigmoidoscopy revealed melanosis of the rectal mucosa without other abnormality. Barium enema showed some small rounded filling defects scattered along the colon, but the caecum was not clearly shown.

Second Operation.—At laparotomy on December 9, 1954, numerous polyps were felt in the caecum and transverse and descending colon. Near the hepatic flexure were two or three large polyps which were thought to be malignant. The small intestine was examined but no polyps were discovered. Total colectomy was performed and the ileum was anastomosed to the rectum.

Pathology.—The resected specimen consisted of the colon and 3–4 in. (7.5–10 cm.) of terminal ileum. Numerous polyps were present in the colon, scattered along its length. The three largest were sectioned and carcinomatous change was demonstrated in one; the other two were benign adenomata.

Convalescence was uneventful. A subsequent barium follow-through examination showed no abnormality in the small intestine. On October 13, 1955, he was readmitted for further examination, as he was complaining of occasional attacks of abdominal colic since the last operation, of frequent loose motions, and the passage of blood on one occasion. He was examined specifically for the presence of any abnormal pigmentation, and for *the first time* melanin spots were noted. These were dark-brown and black discrete spots varying from 1 to 3 mm. in diameter. They were most numerous around the eyes, across the bridge of the nose, on the forehead, and on the nape of the neck. They were relatively sparse around the mouth, but there were some dark bluish patches on the mucosal surface of the lower lips and inside the cheeks. The dorsal surfaces of the hands were covered with light-brown and dark-brown spots; the feet were almost free. No pigment spots were present on the arms, legs, or trunk. When he was asked about the pigmentation he said that it had been present all his life and had, in fact, faded since his boyhood, when he recalled having been taken to hospital for advice concerning the dark spots on his face. He had completely lost touch with his family—both brothers and sisters, and two sons—but he could not recall that any of them had suffered from either pigmentation or abdominal pain.

Apart from the pigmentation no abnormality of importance was discovered. Sigmoidoscopy was repeated, but revealed no abnormality other than the rectal melanosis. Examination was repeated early in 1956 with negative findings.

He remained fairly well until August, 1956, when he reported the passage of blood per rectum. Digital examination discovered an obvious carcinoma of the rectum, confirmed by sigmoidoscopy and biopsy.

Third Operation.—At laparotomy on August 10 the rectal carcinoma was found to be extensively invading the sacrum and was irremovable. The ileo-rectal anastomosis was divided and an ileostomy fashioned.

Case 3

A youth of 18 was admitted to University College Hospital in December, 1946, with a history of recurrent attacks of severe abdominal colic over the last three years. These attacks, not related to meals, were sometimes accompanied by vomiting. The attacks had become more frequent and severe in the last three months. The bowel motions were regular and contained no mucus or blood. A younger brother suffered from occasional attacks of pain of the same type.

On examination, apart from slight fullness in the right hypochondium, no abnormality was found. No pigmentation of the face or lips was noted. A barium meal and follow-through examination showed dilatation of the duodenum with numerous rounded translucencies, particularly of the second and third parts. There was also some dilatation of the upper jejunum.

First Operation.—At laparotomy on December 13 the second, third, and fourth parts of the duodenum were found to be grossly dilated. The upper jejunum was dilated for 2 ft. (61 cm.) and several small solid tumours were felt within the lumen. The lymph nodes in the upper part of the mesentery were enlarged and firm. The rest of the gastro-intestinal tract appeared normal. The duodenum was opened and many polypoid tumours were found arising from the mucosa. One of these was removed for microscopy and the duodenum was closed. Microscopy of the excised tumour showed a benign adenomatous polyp.

In view of his continued symptoms, removal of the polyp-bearing portion of the intestine was decided upon.

Second Operation.—On January 13, 1947, the duodenum and upper 2 ft. (61 cm.) of jejunum were resected together with the head of the pancreas. The distal jejunum was closed and anastomosed to the common bile duct, pancreas, and stomach. At the end of the operation the patient's condition was very poor and he died two hours later.

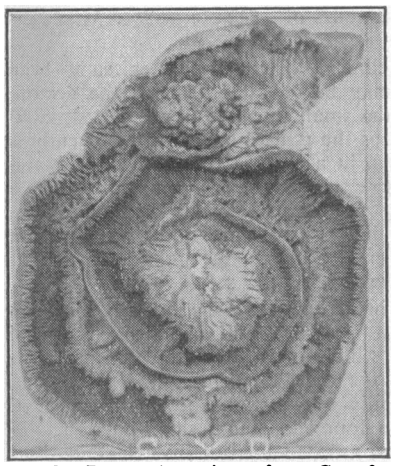

FIG. 2.—Resected specimen from Case 3. Duodenum and upper jejunum bisected to show the polyps arising from the posterior wall.

At necropsy the remaining part of the alimentary tract was carefully inspected but no further polyps were found. The other organs were normal.

Pathology.—The resected specimen (see Fig.) consisted of the whole duodenum and 2 ft. (61 cm.) of jejunum. Arising from the mucosa were 12 polyps over 0.5 cm. in diameter and many smaller ones. Two of the duodenal polyps were very large. Microscopy of the larger tumours showed benign adenomata without evidence of malignant change.

Case 4

A woman aged 55 was admitted to University College Hospital on December 9, 1953, complaining of severe abdominal pain of 10 days' duration, associated with vomiting. Over the past two years she had had several similar attacks which had lasted for six to seven days. She had always been constipated, but more so at the time of the attacks. She occasionally passed blood per rectum independently of the attacks of pain. A cholecystectomy had been performed elsewhere in 1936. No relatives were known to have suffered from similar attacks of pain.

On examination she was seen to be very obese. There was tenderness in the right hypochondrium; no other abnormality was found in the abdomen. Small haemorrhoids were seen on proctoscopy, but no abnormality was felt digitally. No abnormal pigmentation of the mouth or lips was noted.

The abdominal pain subsided spontaneously shortly after admission but returned on December 23, and at that time a vague mass, which appeared to come and go, was felt just above and to the left of the umbilicus. This attack was short, but on December 31 severe pain recurred and on the following day she presented the classical signs of intestinal obstruction with vomiting, distension, and visible peristalsis. A large tender mass could be felt in the left hypochondrium.

Operation.—At laparotomy on January 1, 1954, a jejuno-jejunal intussusception was found about 2 ft. (61 cm.) below the duodeno-jejuno flexure. Reduction was impossible. The intussusception was resected and end-to-end anastomosis carried out. The adjacent jejunum appeared normal, but the rest of the intestine was not explored as the condition of the patient was precarious.

Her post-operative progress was satisfactory until January 13, when she suddenly collapsed and passed a large amount of altered blood per rectum. In spite of immediate blood transfusion her condition steadily deteriorated and she died in a few hours.

At necropsy the end-to-end jejunal anastomosis was sound. A number of epithelial tumours, both sessile and pedunculated, were present for a distance of 1 in. (2.5 cm.) on either side of the anastomosis. Below the anastomosis the small intestine and the colon contained a large amount of dark red fluid blood, but no further tumours were found. It was presumed that the source of the bleeding was one of the remaining polyps.

Pathology.—The resected specimen consisted of an intussusception, the apex being formed by a warty area of mucosa. The epithelium of the intestine involved in the intussusception was studded with numerous oedematous tumours. Microscopy of several of these tumours, and also of those remaining in the jejunum and discovered at necropsy, showed benign adenomata.

Discussion

Cases 1 and 2 are examples of the association between adenomatosis of the gastro-intestinal tract and melanosis of the lips, face, and oral mucosa. Although no pigmentation was noted in Cases 3 and 4 it is possible that it was missed, as we were not aware of the syndrome at the time these patients were seen. The ease with which it may be overlooked is shown by the fact that it was not noticed in Cases 1 and 2 until it was specially looked for with awareness of the syndrome, after the presence of intestinal polyps had already been demonstrated. The possibility of this mistake has been previously pointed out by Wolff (1952). Both these patients were conscious of their abnormal pigmentation; both had previously sought advice concerning it, but neither of them mentioned it until inquiry was made. The first patient (Case 1) subsequently told us that she had been shown to a meeting of the Dermatological Section of the Royal Society of Medicine in 1938, the report of which had been traced (Mitchell-Heggs, 1939).

Diagnosis of small-bowel tumours is usually difficult. Cattell and Colcock (1947) comment that because tumours in this situation are not common they may not be thought of in a patient complaining of mild abdominal cramps or intermittent rectal bleeding. Because of this, any diagnostic aid is useful, and melanin pigmentation is worth looking for in every patient with abdominal pain of obscure origin. Provided that it is borne in mind, it should be easily recognizable. An excellent description of the syndrome has been given by Jeghers *et al.* (1949), and there is little to add to their account; but since familiarity with the condition is not as general as it might be it is worth reiterating some of the features of the syndrome, now usually named after Peutz (Touraine and Couder, 1945).

Pigmentation

Pigmentation is probably present at birth but may not be noticed until early childhood. A case in a patient under 1 year has been reported (Andrews, 1954). Peutz (1921) suggests that the intensity of the pigmentation fades with increasing age and may therefore be less noticeable in older patients. Both our patients (Cases 1 and 2) mentioned this

recession of the pigmentation. Nearly all the reported subjects have been of dark complexion (as were all our four patients), but fair-skinned and fair-haired patients have been reported (Kleitsch *et al.*, 1955; Jones, 1953).

According to Jeghers *et al.* (1949), pigmentation of the oral mucosa is the essential part of the syndrome; the skin may or may not be affected. One of Peutz's cases also showed pigmentation of the rectal mucosa, as did one of our patients (Case 2), but this is uncommon, and melanosis here is, of course, of frequent occurrence apart from this syndrome.

The pigment spots of the mucosa are usually blue-black in colour. They are most numerous on the mucosal surface of the lower lip and cheek, but may be found also on the palate, gums, and the tongue (Jeghers *et al.*, 1949).

The skin pigmentation consists of dark-brown or, occasionally, black spots which remain discrete and do not coalesce. Most of them are about the size of small pinheads, and they are most numerous around the mouth and in a butterfly pattern below the eyes and around the bridge of the nose. Pigment spots may also be found on the extremities, principally on the dorsal surface of the fingers, as they were in our two patients. Under the hand lens the patches have a stippled appearance which was clearly seen in Case 1. Histological examination reveals a collection of melanin distributed in vertical bands through the epidermis (Sherman and Tenner, 1952). A small biopsy was taken from the lip in our Case 1 in 1938, when she sought advice, requesting the removal of the pigmented spots. Microscopy showed "multiple pigmented cells in the deepest layer of the epithelium and melanophores in the fibrous tissue" (Mitchell-Heggs, 1939).

It is important to distinguish these pigmented spots from ordinary freckles. Clinically this distinction can be made by consideration of: (1) The occurrence in people of dark complexion: freckles occur, as a rule, in fair-skinned subjects. (2) The colour: freckles are a lighter brown. (3) The distribution: freckles of the face are most numerous on the cheeks and relatively sparse around the mouth. In this syndrome pigment spots are most numerous in the areas described above and are not usually found on the neck, trunk, or proximal parts of the limbs. (They were, however, numerous on the nape of the neck in our Case 2.) Freckles are not associated with intraoral pigmentation.

Confusion may arise with the pigmentation of Addison's disease (Tanner, 1951), which may also be associated with abdominal symptoms, but the distribution of the pigmentation and, if necessary, biochemical tests should differentiate the two conditions.

Polyposis

The term "polyp" implies a pedunculated tumour. In these cases, however, many of the tumours are sessile, and would be better described as adenomata, to indicate their epithelial origin and avoid possible confusion with other varieties of tumour. In the Peutz syndrome adenomata are scattered throughout the length of the gastro-intestinal tract, but involvement of the small intestine was present in all reported cases, and this may be regarded as an essential part of the syndrome. The small-intestine adenomata may be in the ileum or jejunum, but are usually more numerous in the latter. Adenomata are found in the colon and rectum in rather over half the cases (Peutz, 1921; Jeghers *et al.*, 1949), and tumours in this part of the bowel may be more numerous than in small intestine, as in our Case 2. This syndrome should not, however, be confused with familial polyposis of the large intestine, where the adenomata are confined to the large bowel. This disease of the colon has been very thoroughly investigated; at St. Mark's Hospital 60 colonic-polyposis families have been studied, but no case has been seen exhibiting the melanin pigmentation here described (C. E. Dukes, 1957, personal communication). Adenomatous polyps have often been found in the stomach of patients with the Peutz syndrome (Jeghers *et al.*, 1949; Tanner, 1951). Ravitch (1948) reports the case of a patient whose whole gastro-intestinal tract from cardia to anus was studded with polyps; however, no pigmentation was noted in this case. In two of Peutz's patients polyps were also present in the nasopharynx.

The symptoms produced by these tumours have been classified by Olson *et al.* (1951) as: (1) symptoms of obstruction, (2) bleeding, and (3) symptoms produced by local irritability of the intestine. The first symptoms most often appear between 10 and 30 years of age, although the diagnosis has been made in many younger and a few far older patients.

Obstruction, which may be due to obturation of the intestine, but more often to intussusception, causes spasmodic abdominal pain, which may be associated with vomiting. Intussusception in general is rare in adult life, 78% of cases occurring before the age of 1 year (Williams and Williams, 1949), and when it does occur in adults a tumour of the bowel is nearly always the cause. The intussusception tends to be a chronic one, less dramatic than the infantile variety, but it may become acute later.

Frank bleeding is most often due to polyps in the colon, but sometimes the origin is in the small intestine. If ileal tumours are responsible the blood is usually dark red, but jejunal tumours will lead to tarry stools. In many cases bleeding is not severe enough to be noticed but may cause an iron-deficiency anaemia.

Local irritability of the small intestine may lead to diarrhoea, and duodenal tumours often cause symptoms suggestive of a peptic ulcer.

The difficulty of clinical diagnosis has already been stressed. Radiology may be of little help, as the demonstration of polyps in the small intestine is notoriously difficult, although sometimes the typical appearances of chronic intussusception are seen in a barium follow-through examination. Polyps in the rectum can be seen on sigmoidoscopy easily enough and gastric polyps may be seen on gastroscopy (Tanner, 1951), but tumours are not always present in these sites, and, even if they are recognized, do not, of course, indicate involvement of the small bowel.

The only easy way of arriving at a diagnosis is therefore by recognition of the presence and significance of the typical pigmentation, which often obviates the need for repeated investigation of these difficult cases. Jeghers *et al.* (1949) reported that only one person showing the typical pigmentation had been found in whom small-bowel polyposis had not been demonstrated by full investigation short of laparotomy. Wolff (1952) sums up the position when he says, "Dark pigmentation on the mucosa of the lips and mouth in a patient without Addison's disease, and with a history of abdominal pain, strongly suggests polyposis of the small intestine."

Family History

There is a strong tendency for this syndrome to occur in near relatives. Crone and Light (1954) have reported two triplets with the full syndrome; the third showed the pigmentation, but the presence of polyposis had not been demonstrated at that time. However, several apparently sporadic cases have also been reported, and a family history does not appear to be an essential part of the syndrome. No such history was obtained from either of our two patients. Although there was a suggestion that a brother of Case 3 suffered from intestinal colic, no pigmentation was noted in this patient.

The inheritance of familial polyposis of the colon has been very fully worked out (Dukes, 1952a), but it has not been possible to analyse the inheritance of the Peutz syndrome so thoroughly owing to the comparatively small number of known cases. However, it probably follows a similar genetic pattern and is inherited as a Mendelian dominant which is not sex-linked (Jeghers *et al.*, 1949); new cases may occur as a result of gene mutation.

Risk of Malignant Degeneration

The complications of haemorrhage and intussusception have been discussed. The only other important complication

is that of development of carcinoma in a previously benign adenoma. This risk is high and well recognized in the case of familial polyposis of the colon, in which condition the average age of diagnosis of carcinoma is about 35 years, and the ultimate development of carcinoma is almost invariable if the polyposis is left untreated (Dukes, 1952b). Gastro-intestinal polyposis of the Peutz type has not in the past been considered so seriously from this point of view. In order to obtain more information on the incidence of carcinoma I have looked through all the published case reports. The Table summarizes those cases where adequate details have been given concerning the distribution and histology of the intestinal tumours. Including our two patients (Cases 1 and 2) this gives a total of 67 patients for analysis. The occurrence of carcinoma of the gastro-intestinal tract is recorded in 16 of them, an incidence of nearly 24%. In 13 of these cases the malignant tumour was situated in the small intestine, an incidence of about 19%. In the remainder the carcinoma developed in the colon or rectum. These figures are startling, especially when it is considered that the recorded incidence of carcinoma would probably be higher if all polyps removed were subjected to routine serial section (River *et al.*, 1956). Vary (1956) also comments that many of these patients die from the effects of multiple intussusception or anaemia and thus do not reach the age of maximum incidence of cancer.

Clearly the polyposis of the Peutz syndrome must be regarded as a precancerous condition.

Summary of Cases

Author	Sex and Age of Patients	Histology of Tumours
Peutz (1921)	M15	Adenocarcinoma (jejunum)
van Dijk and Oudendal (1925)	M16	Benign adenomata
	F 25	,, ,,
Foster (1944)	M43	Adenocarcinoma (jejunum)
	F 16	,, (ileum)
Ravitch (1948)	F 16	Benign adenomata
Jeghers *et al.* (1949)	F 14	,, ,,
	F 39	,, ,,
	F 22	Adenocarcinoma (ileum)
	F 30	Benign adenomata
	F 9	,, ,,
	M16	,, ,,
	F 15	,, ,,
	M 8	,, ,,
	F 16	,, ,,
	M20	,, ,,
Bradford and Danzig (1950)	M15	,, ,,
Roux (1950)	M20	,, ,,
Behrer and Simril (1951)	M14	,, ,,
Fisher (1951)	M 7	Adenocarcinoma (jejunum)
Lima Basto (1951)	M22	Benign adenomata
Tanner (1951)	F 17	,, ,,
Basu (1952)	F 25	Adenocarcinomata (jejunum and ileum)
Schaffer and Sachs (1952)	F 16	Benign adenomata
Wolff (1952). (Previously reported by Cope, 1922)	M50	,, ,,
Hunter and Wilson (1953)	F 31	,, ,,
Jones (1953)	F 22	,, ,,
	F 56	,, ,,
	F 20	,, ,,
	F 32	,, ,,
Kaplan and Feuchtwanger (1953)	M16	,, ,,
Kitchin (1953)	F 26	,, ,,
	F 35	,, ,,
Ortiz *et al.* (1953)	F 9	,, ,,
Rezza and Campani (1953)	F 4	,, ,,
Young (1953)	M 5	,, ,,
Brayton and Norris (1954)	F 15	Adenocarcinoma (jejunum)
Bruwer *et al.* (1954)	F 27	Benign adenomata
Crone and Light (1954)	F 8	,, ,,
	F 12	,, ,,
Rankin and Laird (1954)	M 6	,, ,,
	M31	,, ,,
Savage (1954)	M28	,, ,,
Smith (1954)	F 29	Adenocarcinoma (ileum)
Troxell (1954)	M77	Adenocarcinoma (rectum) (histology of small-intestine tumours not detailed)
Tseng and Braunstein (1954)	F 21	Benign adenomata
Walker-Brash (1954)	M28	,, ,,
	M12	,, ,,
Weber (1954)	F 15	Adenocarcinoma (jejuno-ileal)
Young (1954)	F 16	Benign adenomata
	F 32	,, ,,
Berkowitz *et al.* (1955)	F 11½	Adenocarcinoma (ileum)
	F 26	Benign adenomata
	F 31	Probably benign adenomata (no definite histology given)
Freeman and Ravdin (1955)	M35	Adenocarcinoma (ileum)
Kleitsch *et al.* (1955)	M23	,, (jejunum)
Pool *et al.* (1955)	M13	Benign adenomata
	M 4	,, ,,
Sohmer and Cayer (1955)	M37	Adenocarcinomata (colon and caecum)
Stewart, and Storey (1955) (previously reported by Perry and Zuska (1950) and Sherman and Tenner (1952)	M16	Benign adenomata
Brockhaus and Jochmus (1956)	F 12½	Adenocarcinoma (jejunum)
River *et al.* (1956)	F 40	Benign adenomata
	M63	,, ,,
van Wyk and Glen (1956)	F 19	,, ,,
	M16	,, ,,
Bailey (present cases)	F 35	,, ,,
	M56	Adenocarcinomata (colon and rectum). Small-intestine tumours not examined microscopically

Treatment

In the past it was agreed that no treatment was indicated in this condition until the need was determined by symptoms, except in the case of colonic polyps accessible to sigmoidoscopic removal. Intussusceptions were treated by emergency operation and at the same time the bowel was examined for the presence of polyps, the larger ones being removed by enterotomy or resection of short lengths of intestine.

Recognition of the precancerous nature of this syndrome raises the question of whether a more aggressive policy should not be adopted. If the patient is known to be suffering from polyposis, should surgery be undertaken in the absence of serious symptoms; or, further, should laparotomy and any further procedure necessary be undertaken on recognition of the pigmentation alone, in the absence of any definite evidence of polyposis? In the case of familial polyposis of the colon, surgery for prophylaxis against cancer is now accepted, and many of these patients are treated by total colectomy, ileo-rectal anastomosis, and control of polyps in the rectal stump by regular sigmoidoscopic examinations. There is clearly a need for similar prophylactic surgery when dealing with the more generalized polyposis of the Peutz syndrome, but if the principle is accepted two questions must be answered—What type of surgery? and When should it be carried out?

In a few cases the polyps are localized to comparatively short lengths of intestine, resection of which is possible, although, since it is easy to overlook small polyps when palpating the unopened intestine, this will not always result in removal of all the tumours. An example of this is provided by our Case 4. If the polyps are more generalized resective surgery is contraindicated by the need to preserve enough small intestine for adequate function. Camp and Lesser (1952) resected half the duodenum, the whole jejunum, and half the length of the ileum without any apparent ill effect, but this must be regarded as exceptional; in general, resection of much shorter lengths of small intestine will result in severe jejuno-ileal insufficiency. Resection of the colon, removal of a short length of small intestine, and ileo-proctostomy are permissible where the colon is extensively involved and only a few polyps are situated in the small bowel, which is occasionally the state of affairs—for example, our Case 2. In other cases some alternative method of clearing the intestine of these dangerous adenomata must be adopted. Such a method has been suggested and carried out by Vary (1956). Briefly, the procedure is as follows.

A 1½-in. (4-cm.) longitudinal enterotomy is made on the antimesenteric aspect of the jejunum about 10 in. (25 cm.) below the duodeno-jejunal flexure. Through this, tissue forceps are passed up the lumen of the intestine and made to

grip the mesenteric border as high up as possible. By a combination of traction on the forceps and pressure from without the jejunum is intussuscepted and made to protrude through the enterotomy opening, so that the mucous surface is facing outwards, and is available for inspection and removal of any adenomata. After reduction the intestine below is brought upwards through the enterotomy in a similar manner and cleared of polyps in turn. The enterotomy is then closed transversely. The process is continued seriatim down to the ileo-caecal junction or into the colon if necessary. Vary states that this procedure causes little disturbance to the patient and recovery is uneventful. This type of operation appears to be the most practicable method of cancer prophylaxis in this disease, but it is unlikely to be entirely effective, as it is easy to overlook tiny tumours and also because new adenomata may develop in the future. The suggestion that the procedure could be repeated every few years is not likely to meet with general acceptance. Certainly following such an operation, or indeed any operation in this disease, the patient must be kept under observation and re-examined at frequent intervals.

The next problem is to decide *when* surgery should be carried out. In the 16 patients developing carcinoma (see Table) the average age of diagnosis of malignant disease was 27 years, or, if the three patients with cancer of the large intestine are excluded, 20 years. From these figures alone it might be argued that clearance of the polyps should be undertaken at an arbitrary age of about 18 years. However, exploration at this age might well be negative, since, although this is a congenital syndrome, it appears likely that in many cases the polyps do not develop until a comparatively late age; it is, for example, difficult to believe that the polyps had been present for very long in our first patient (Case 1), as she had no intestinal symptoms at all until the age of 33 years—that is 17 months before her abdominal operation. For the time being, therefore, the question of the timing of the operation must remain unsolved, but it is suggested that where symptoms have been present for more than a few months a clearance of as many adenomata as possible should be carried out along the lines indicated above, or, if an emergency operation is required owing to the occurrence of intussusception, a similar general clearance of polyps should be attempted where the general condition of the patient permits.

To settle the question, an idea of the average duration of symptoms before the development of malignant degeneration is required, and in order to obtain further information it is desirable that all cases of this syndrome should be reported, as only a few cases are likely to be seen by any one group of surgeons. Full details are particularly required in cases complicated by the development of carcinoma. Details of long-term results following prophylactic operations are also necessary in order to assess their effectiveness.

Other Reported Cases

The Table includes only those cases where full details are available. Other patients with the syndrome have been reported by Peutz (1921), Touraine and Couder (1945), Ravitch (1952), Andrew (1953), Andrews (1954), Goldberg and Goldhaber (1954), Bortz and Bethell (1955), Hafter (1955), Horzelowa and Stapiński (1955), Exinger (1956), Klostermann (1956), and Vary (1956). The reason for the exclusion of these cases from the Table is in most instances lack of pathological information concerning the polyps or because the small intestine had been investigated only by *x*-ray examination and not at operation. With the 67 cases already included in the Table, this brings the total number of reported cases which I have been able to trace up to 80. A further case described by Renyard (1951) is almost certainly an example of the Peutz syndrome, but the description of the pigmentation does not correspond to the typical picture. The two cases described by Cronkhite and Canada (1955), in which gastro-intestinal polyposis was associated with diffuse pigmentation, alopecia, and atrophy of the fingernails, appear to be examples of another syndrome as the authors themselves suggest. Several other probable examples of the Peutz syndrome have been reported, but since they cannot be regarded as certain they are not listed.

Summary

Four cases of polyposis of the gastro-intestinal tract are reported. Melanin pigmentation of the mouth, lips, and digits was noted in two of these cases, which are considered to be examples of the syndrome described by Peutz (1921).

The essential features of this syndrome are: (*a*) dark pigmentation of the buccal mucosa of lips and cheeks, and often of the skin of the face and digits; and (*b*) multiple adenomata of the gastro-intestinal tract with involvement of the small intestine in all cases.

The main symptoms of tumours of the small intestine are intermittent obstruction and bleeding. The difficulties of diagnosis are discussed and the usefulness of the pigmentation as a diagnostic aid is emphasized.

Sixty-seven reported cases of the Peutz syndrome are tabulated. The incidence of malignant tumours is 24%.

The treatment of the syndrome is discussed. Elective surgery for prophylaxis against cancer is justified when symptoms attributable to polyposis are present. Removal of the tumours may be accomplished by serial enterotomies or resection of short lengths of intestine.

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HYPOPITUITARISM WITH CONSECUTIVE DEVELOPMENT OF DIABETES MELLITUS

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The first convincing demonstration of the importance of the anterior part of the pituitary gland in diabetes mellitus was given in 1931 by Houssay and Biasotti, when they showed that the diabetes which followed pancreatectomy in dogs could be alleviated by hypophysectomy; and the "Houssay dog" formed the basis for a great deal of experimental work in the years that followed. It was also found that if anterior pituitary extracts were injected into dogs thus operated on the diabetes reverted to its former severity. Later, Young (1937) found that administration of pituitary extract to adult dogs for a certain length of time led to the development of diabetes mellitus. The occurrence of hyperglycaemia and glycosuria in a proportion of patients with acromegaly had of course been recognized for many years.

In the last twenty years the role of the pituitary and of other endocrine glands in the aetiology of diabetes has become increasingly obvious, so much so that Himsworth (1949) declared that diabetes could no longer be regarded as a single entity but as a syndrome. Nevertheless there are many points still not fully understood, among which should be mentioned the part played by the glands of internal secretion in the production of some of the complications of the disease.

The Houssay phenomenon, first described in dogs, has been reported in man on various occasions. In each of these cases pituitary insufficiency has developed in patients known to have had diabetes for a varying length of time; the pathological lesions have been diverse and have included infarction, tumour, and abscess. It is extremely rare, however, for the sequence of events to be reversed, and we have been able to find only one previous report of such a condition.

Case Report

The patient was first seen by us in September, 1953, at the age of 45, when he was referred by his doctor with a request for gastro-intestinal investigations. He stated that for about ten years he had suffered from recurrent attacks of pain in the epigastrium and right hypochondrium accompanied by vomiting; he also complained of backache for three years, with difficulty in stooping, and a sensation of locking in the small of the back. As he was extremely deaf his wife amplified the history and revealed that since her marriage to him in 1943 she had known that he was sexually underdeveloped. She stated that during their married life her husband had seldom shown any desire for intercourse, and when he attempted coitus he was unable to achieve erection. The patient himself was quite co-operative during interrogation, but seemed unaware of the significance of many of the questions. He did, however, volunteer the opinion that "it was all the result of self-abuse"; he stated that during his middle teens he had occasionally masturbated and had had seminal emissions. This was the only fact ever obtained that might give some hint regarding the duration of the pituitary deficiency.

In 1947 he was examined by an ophthalmologist because of iritis and early keratitis in the right eye, and the blood Wassermann reaction was found to be strongly positive; his brother's W.R. was also positive, and a presumptive diagnosis of congenital syphilis had been made at that time. The patient's wife had known him for about eight years before marriage and thought that "he had always looked much the same." In view of this story he was admitted for endocrinological study.

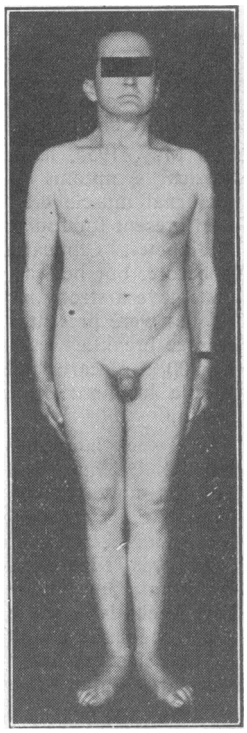

FIG. 1.—Photograph of patient; body hair absent and genitals underdeveloped.

In appearance the patient looked pale; his face was smooth and hairless, and the skin of the body generally rather dry. No axillary sweating was observed; there was no cutaneous or mucosal pigmentation. Hair was completely absent from axillae, chest, abdomen, and thighs, but a few fine downy hairs were present on the pubic region. Both testes were in the scrotum, but were soft and only the size of a pea; the penis approximated to that of a prepubertal boy (see Fig. 1).

The lungs, cardiovascular system, and alimentary system were clinically normal. The blood pressure was 140/80. No neurological abnormality was noted except that the left pupil was a little larger than the right; both reacted to light and on convergence. The fundi were normal. Moderate dorsal kyphosis and an exaggerated lumbar lordosis were present.

Mentally he was a placid, amiable individual, and took little interest in his surroundings or in his own condition. He showed no diffidence in exposing his body for examination.

Radiological and Laboratory Studies.—*X*-ray examination of the skull showed that the pituitary fossa was normal. The lumbar spine showed generalized osteoporosis with osteoarthritic change between the spines of L 3 and 4; there was slight wedging of the bodies of D 11 and 12 with minimal osteoarthritic changes; the appearances suggested old fracture. No abnormality was noted in the epiphyses of the long bones. 17-Ketosteroid excretion, 2 mg. a day. Fasting blood sugar, 85 mg. per 100 ml. Glucose-tolerance test, normal (see Fig. 2). Serum electrolytes: sodium, 315 mg.; potassium, 18 mg. chlorides, 640 mg. per 100 ml. Serum cholesterol, 200 mg. per 100 ml. Serum proteins, total 6.1 g. per 100 ml. (albumin 4.2 g., globulin 1.9 g.).