Peutz-Jeghers Syndrome: Its Natural Course and Management[1]

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Abstract Two hundred and twenty-two patients with Peutz-Jeghers syndrome were ascertained in Japan between 1961 and 1974 through two nationwide surveys, medical literature, and personal examinations. Genetic analysis was made of this group as well as 102 follow-up cases. The average age at diagnosis was 23 in males and 26 in females, with male to female ratio of 1:1.13. Presenting complaints of 170 patients included obstruction (42.8% of patients), abdominal pain (23.4%), rectal bleeding (13.5%), extrusion of polyp (7.2%). Diagnosis of 52 patients was based on melanin pigmentation. Intussusception occurred in 46.9% of the patients, most often in the small intestine. Polyps occurred in the stomach in 108 patients (48.6%), small intestine, 142 patients (64%), colon, 118 patients (53.2%) and rectum, 71 patients (32%). Among the 222 patients, cancer was histologically verified in 28. Fifteen early cancers occurred (3 gastric, 8 small intestine, 4 colon), and 11 advanced cancers (3 gastric, 1 small intestine, 6 colon, and 1 both colon and small intestine). Mortality was lower than in patients with familial polyposis coli but higher than in the general population. Conservative surgical management, planned medical follow-up, and the need for a national registration system are stressed.

The Peutz-Jeghers syndrome (P-J syndrome) is a hereditary disorder in which gastrointestinal polyposis is associated with characteristic skin pigmentation. It was established as an entity by Jeghers, McKusick, and Katz in 1949 (1). The syndrome is considered to be rare, few cases having been reported even half a century after the original description by Peutz in 1921 (2). Although much has been learned about its clinical, genetic, and pathologic features, its natural course is still largely uncertain.

In Japan, since the first presentation of a case of P-J syndrome in 1955 by our late colleague, K. Nagasu (3), increasing numbers of case reports have appeared. In 1961 we initiated a nationwide survey of the P-J syndrome as part of an epidemiologic study of polyposis of the digestive tract (4, 5). The purpose was to elucidate the natural course of this disorder and to evaluate management.

[1] *Editorial note*: This study of the Peutz-Jeghers syndrome is part of an overall investigation of hereditary polyposis being conducted in Japan by Dr. Utsunomiya and his colleagues. For the sake of comparison, similar methods are being used in this study and a study underway in the Mid-Atlantic States by the Divisions of Medical Genetics and Gastroenterology, Department of Medicine, The Johns Hopkins University School of Medicine.

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MATERIALS AND METHODS

Three sources were used for ascertainment of patients with the P-J syndrome: (1) registration, (2) family history, and (3) cases reported in the Japanese medical literature (Table I).

In all, 84 cases in 79 families have been registered (*registered cases*), including 8 cases examined by us and 76 others ascertained through national surveys. The eight patients with the P-J syndrome whom we have personally examined (*personal cases*) are from seven families. Six of these patients have been followed for more than ten years. The chronology of examinations and surgery is shown in Figure 1 and the pedigrees in Figure 2.

The nationwide surveys were carried out in 1961 and 1972 by means of questionnaires to physicians at approximately 1,000 general hospitals. Data concerning the diagnosis and treatment, family history, and personal identification were accumulated for 76 members of 72 families (*survey cases*). About 60% of the *registered cases* were found to have been reported already in Japanese medical journals.

Complete pedigrees were constructed to include at least first, second, and third degree relatives. Years of survival and dates of death of each family member were confirmed by consulting the Family Register Records (*Koseki*). Confirmation of the diagnosis of the P-J syndrome in family members was

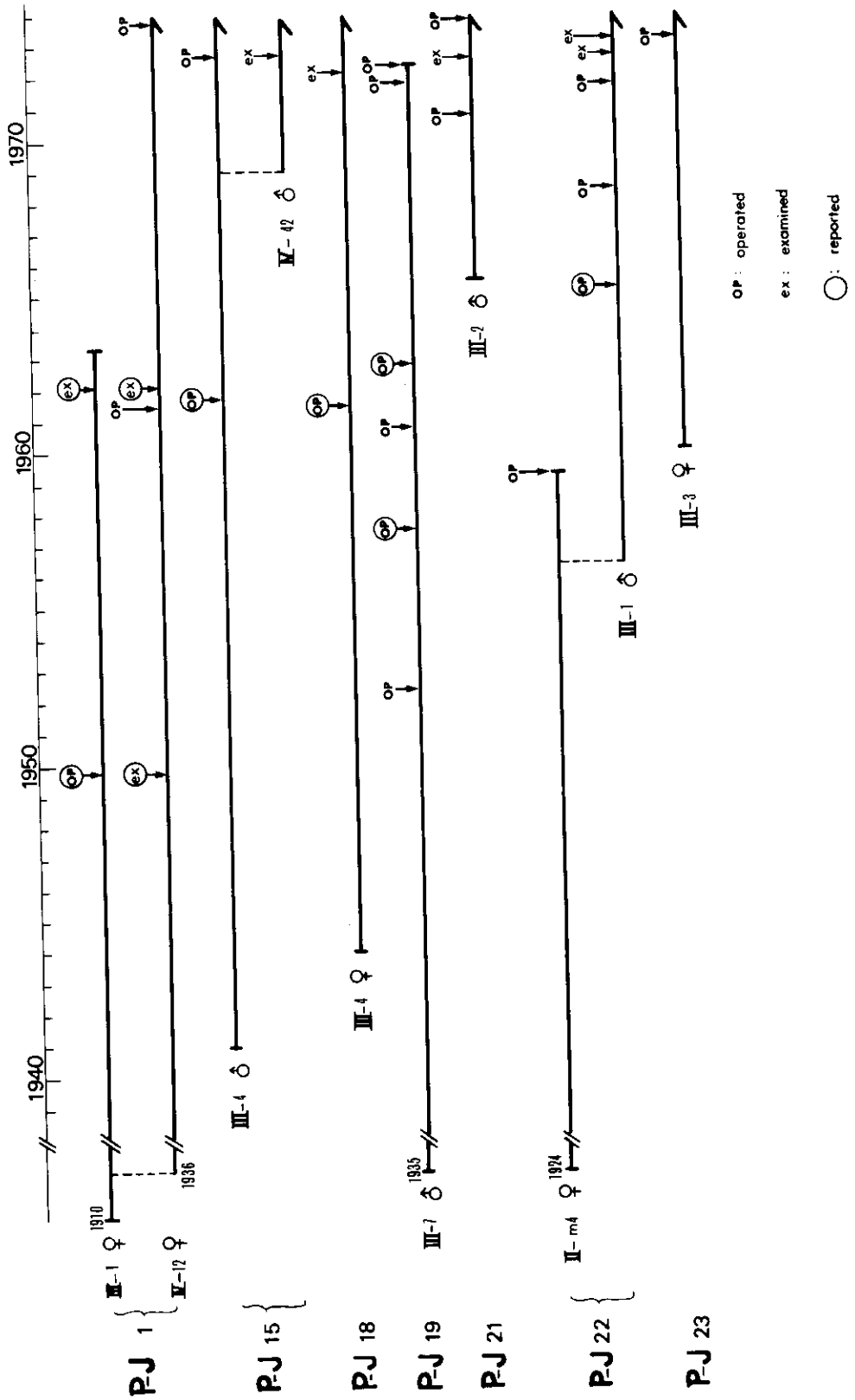

Fig 1. Medical histories of *personal cases*, 1910-1974.

TABLE I

Source of Information

	Recorded cases No. of cases		Recorded cases No. of families		Follow-up cases No. of cases	
Registered cases	84		79		70	
Personal cases		(8)		(7)		(8)
National Survey Cases		(76)		(72)		(62)
Family history cases	–		–		32	
Literature cases	138		113		–	
Total	222		192		102	

obtained by communication with the family or with their attending physicians, and causes of death during the past 27 years were confirmed by death certificates.

As of 1974, the outcome had been determined in 70 of the 84 *registered cases*. In their families 32 relatives have also been confirmed as affected, and are being followed (*family history cases*). They include 13 parents, 6 sibs, 5 offspring and 8 other relatives. Thus a total of 102 patients with the P-J syndrome (*follow-up cases*) are included in the follow-up section of this study (Table I).

An extensive review of the Japanese medical literature revealed 196 cases of the P-J syndrome.[2] After excluding doubly reported cases (e.g., P-J 1 and P-J 19 of Fig 2) and the cases already identified among the *registered cases*, clinical as well as genetic information was obtained for the remaining 138 cases (*literature cases*).

Clinical analyses were made of 222 *recorded cases* (those for which clinical information was available), which included both *registered* and *literature cases*. The natural course of the disease was analyzed in the 102 *follow-up cases*. Both groups were used for genetic analyses.

[2] References to Japanese case reports (until the beginning of 1974) used in this study are available on request to Dr. J. Utsunomiya.

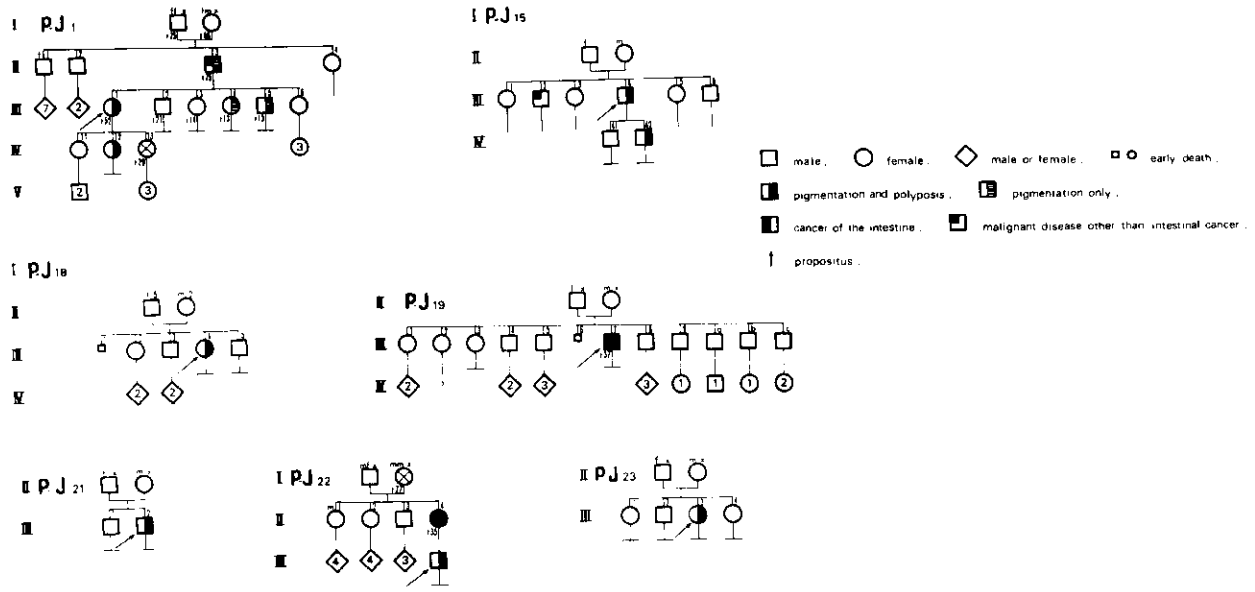

Fig 2. Pedigrees of 7 *personal cases*.

RESULTS

I. Clinical Manifestations and Course

Age at diagnosis: While the average age at diagnosis differed little between the sexes (23.0 years of age in males and 26.0 years of age in females), the age distribution curve demonstrates a clustering of the male cases at younger ages of diagnosis. This pattern is in contrast to that in familial polyposis coli which peaks at later ages for males (6) as shown in Figure 3.

Sex ratio: The male-to-female ratio is 1:1.13. This also differs from familial polyposis coli in which the ratio is 1:0.61 (6).

Presenting complaints: One hundred and seventy (76.6%) of the *recorded case* patients visited their physicians with the chief complaint of gastrointestinal symptoms such as those of (1) obstruction in 95 cases (42.8%), (2) abdominal pain in 52 cases (23.4%), (3) bloody stool in 30 cases (13.5%), and (4) anal extrusion of the polyp in 16 cases (7.2%). The remaining 52 cases (23.4%) were diagnosed primarily because of melanin pigmentation.

Complications: The most serious complication was intussusception, occurring in 105 cases (46.9%), mostly in the small intestine (95.2% of the cases).

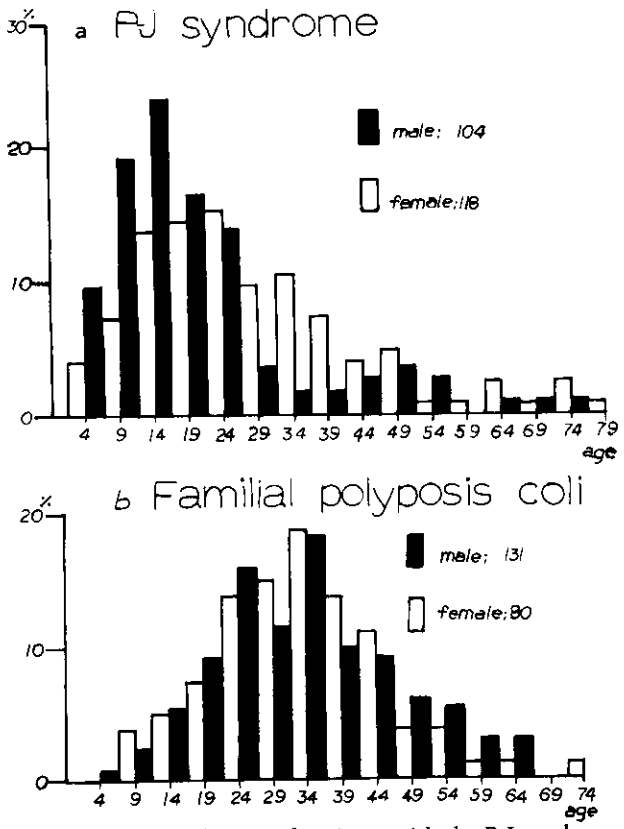

Fig 3. Age distribution of patients with the P-J syndrome (a) and familial polyposis coli (b).

Intussusception in the stomach was described in one patient and four had colonic intussusception.

Intussusception of the small intestine may occur in the jejunum and ileum, and sometimes simultaneously in several locations (see Fig 12a). Since intussusception often recurs, an upper GI series may reveal a dilated small intestine although no clinical symptoms are present (Fig 4a). Severe chronic malnutrition may ensue if treatment is not instituted as seen in case P-J 23, III-3 (Fig 2) who regained her weight loss of 12 kg several months after the removal of a polyp which had caused intussusception.

Polyposis: Polyps were detected in 195 (87.8%) of the *recorded cases*. They occurred throughout the digestive tract with the exception of the esophagus. Distribution of polyps in the different segments of the gastrointestinal tract is shown in Table II, and is compared with data from Bartholomew's series (7, 8). It is of interest that his series revealed a particularly high frequency of polyps in the small intestine (96.2%) as compared to ours (64.0%) and that in our series polyps of the stomach and colon occurred about twice as frequently as in his series.

The smaller polyps are sessile, the larger ones pedunculated. We believe that polyps in the stomach are rarely pedunculated (Fig 5b). The P-J polyp has a characteristic lobulated appearance, sometimes resembling the cerebral convolutions (see Fig 6a) and is easily differentiated from other types of gastrointestinal polyps. The number of polyps varies from one to 10-20 per gastrointestinal segment (Figs 4b, 6a). The colon is never carpeted with polyps as it may be in familial polyposis coli. The growth rate of polyps varies. Often in young patients polyps seem to grow rapidly as seen in P-J 22, III-1 (Figs 2 and 7) in whom polyps developed from a radiologically undetectable size to a considerable size in seven months. P-J 19, III-7 (Fig 2) showed another extreme example of the potential for polyp production: during a 20-year period, he underwent five resections in the small and one in the large intestine due to the polyps, in five different hospitals. On the other hand, polyp production may remain stationary for a long time as seen in P-J 18, III-4 (Fig 2) in whom a single small polyp was detected in the sigmoid colon during a thorough gastrointestinal examination 11 years after her initial treatment. Figure 8 shows polyps of different growth rates occurring in one individual. (Histologic details will be discussed in a separate paper.)

Occasionally polyps may disappear or slough off spontaneously. Anal prolapse of a polyp has often been reported. One of our patients (P-J 15, III-4, Fig 2) had two polyps in the pyloric antrum, confirmed either by x-ray or endoscopy but not present at endoscopy 11 years later.

Malignant changes of the polyp: An important clinical

TABLE II

Distribution of Polyps in the *Recorded Cases* and in Bartholomew's Series (7,8)

Site of Polyps	Present series (222 cases) No. of cases	%	Bartholomew's series (182 cases) No. of cases	%
Stomach	108	48.6	44	24.2
Small intestine	142	64.0	175	96.2
Duodenum	47	21.2	30	16.5
Jejunum	95	42.8	117	64.3
Ileum	73	33.0	95	52.5
not stated	–	–	18	9.9
Large intestine	132	59.5	?	?
Colon	118	53.2	53	29.1
Rectum	71	32.0	44	24.2
Polyps not detected or location not stated	27	12.2	–	–

issue is the possibility of malignant transformation of polyps. Among the 222 *recorded cases*, malignancy was histologically confirmed in 28 (12.6%). These included 15 examples of "early cancer" (3 in the stomach, 8 in the small intestine, 4 in the large intestine) and 11 of "advanced cancer" (3 in the stomach, 1 in the small intestine, 1 in both small and large intestines, and 6 in the large intestine).

We agree with Bartholomew that the typical polyp in the P-J syndrome is hamartomatous and that

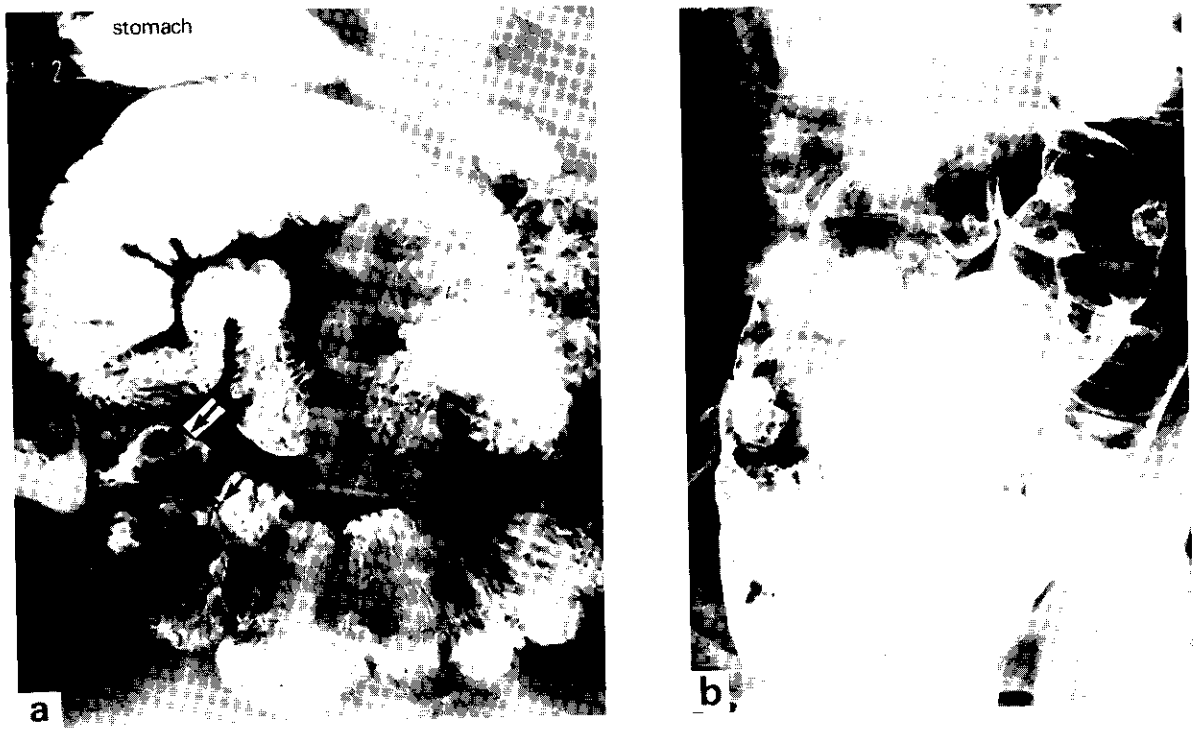

Fig 4. X-ray features of the intestine of case P-J 15, III-4. (a) Barium meal x-ray showing the remarkably dilated jejunum and shadows of polyps (indicated by arrows). (b) Barium enema x-ray showing multiple pedunculated large polyps in the sigmoid colon.

the presence of mitotic figures or heterotopic accumulations of glandular structures in the mucosal layer should not necessarily be considered evidence of malignant transformation of the polyp. We, therefore, feel that inclusion of the above-mentioned cases as instances of "early cancer" may not be valid in all cases. However, we must be aware of the possibility of malignant transformation even in polyps of the small intestine because of the following evidence. We observed a microfocus highly suspicious of malignancy in polys from two *personal cases*. One was a small localized lesion found in the superficial part of one of the jejunal polyps of case P-J 15, III-4 (Fig 2). It showed marked cellular atypia with multiple mitotic figures, suggesting early malignancy, as shown in Figure 6b. The other was found in one of the polyps in the jejunum of case P-J 19, III-7 (Fig 2), with the lesion suggesting invasion of gelatinous carcinoma into the stalk and muscle layer rather than simply an ectopic duct as part of the hamartoma (Fig 9).

Bartholomew et al noted in 1962 that carcinomatosis resulting from one of these gastrointestinal polyps had not been recorded as the cause of

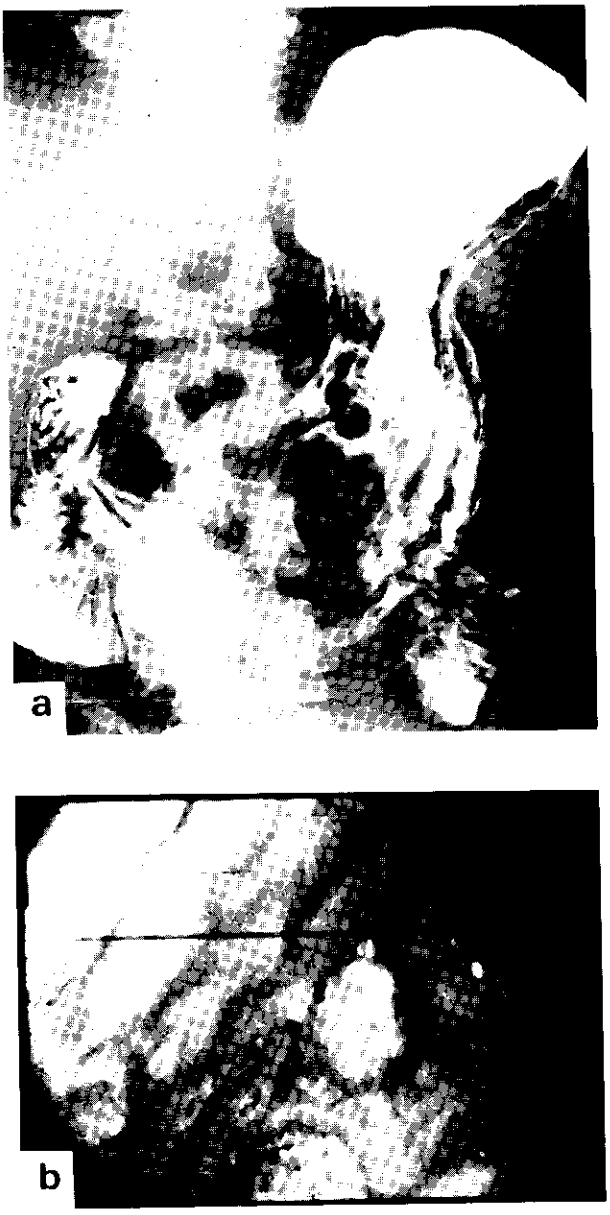

Fig 5. X-ray (a) and endoscopic (b) appearance of gastric polyps of case P-J 23, III-3.

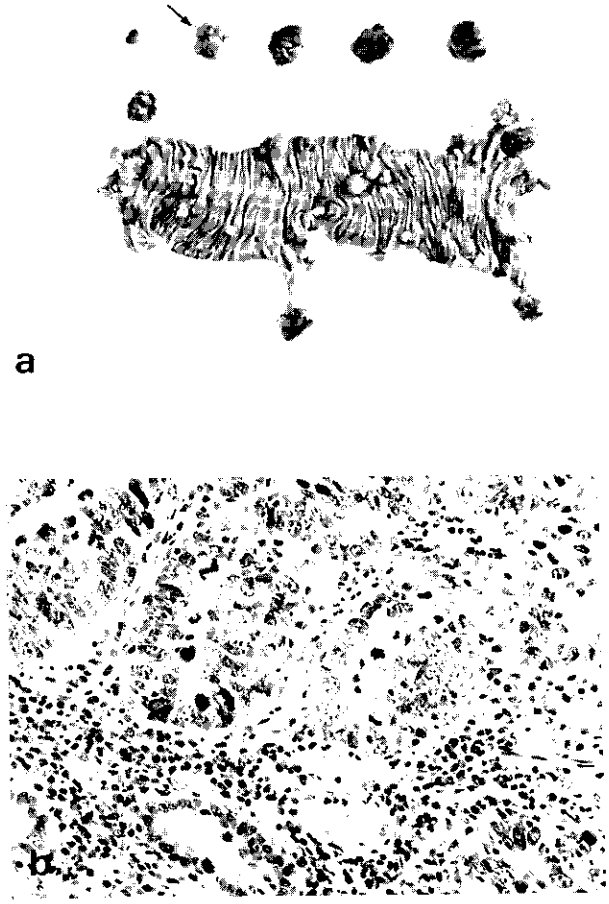

Fig 6. Surgical specimens from case P-J 15, III-4. (a) Six polyps removed from the small intestine and a segment of the descending and sigmoid colon. Segmental colectomy was performed because of continuous bleeding; fiberscopic polypectomy can now be used instead. (b) Microscopic features (×300) of a superficial part of one of the jejunal polyps indicated by an arrow in (a). Note marked cellular atypia with multiple mitotic figures highly suggestive of malignant lesion.

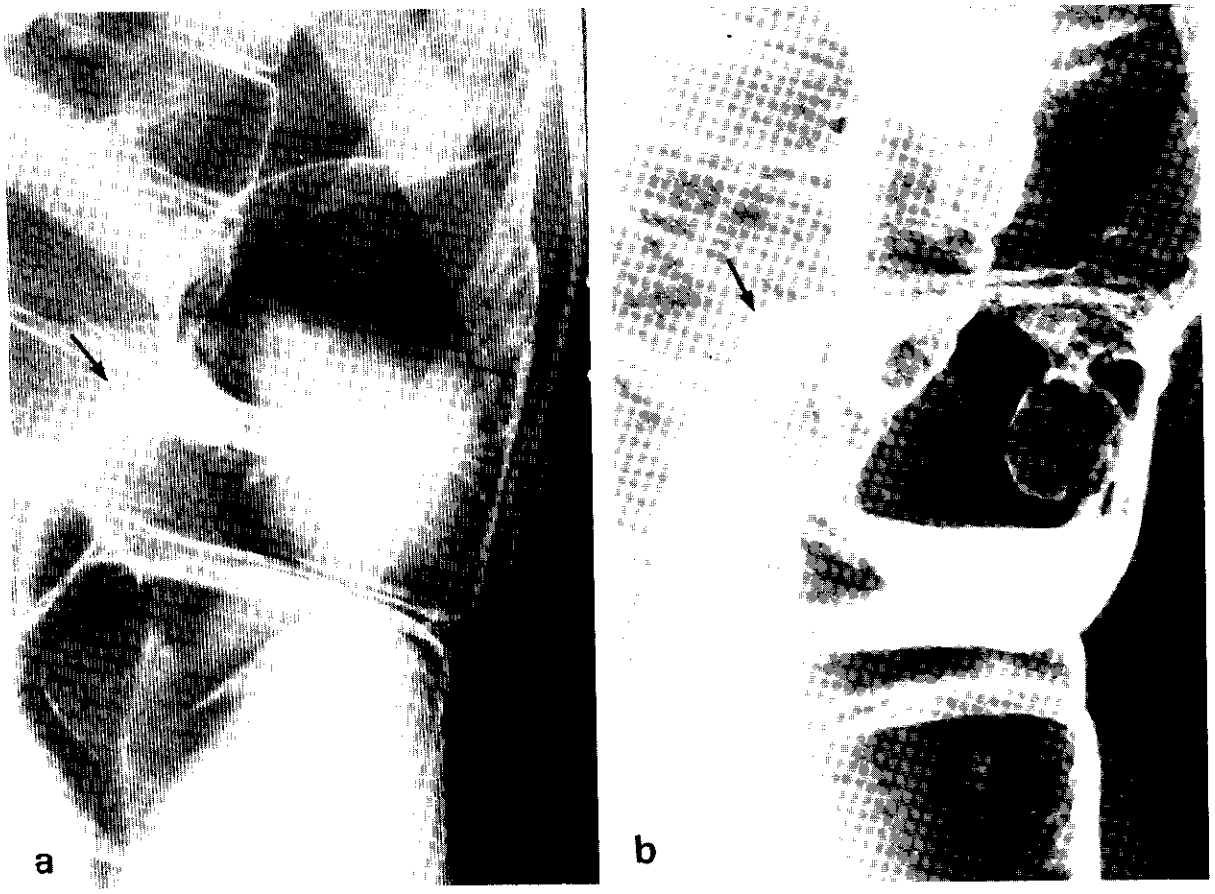

Fig 7. Barium enema x-rays of case P-J 22, III-1. (a) taken 26 July 1972 and (b) 3 March 1973. Arrow points to a small diverticulum indicating that the two pictures were taken at the same location in the descending colon.

death in any of approximately 182 patients reported in the literature (8). Although a diagnosis of advanced cancer in the P-J syndrome does not necessarily indicate that it developed in a polyp, it is noteworthy that so many instances of advanced cancer in various parts of the gastrointestinal tract occurred in the present series. The cases of advanced stomach cancer in our series occurred in very young persons, 13, 14, and 17 years of age. Two examples of advanced cancer in the small intestine were confirmed histologically. An association with cancer of the large intestine will be discussed below. Advanced cancer has been observed rarely in small intestine with multiple polyps. An explanation may be that 76.7% of the patients visited their physicians early for symptoms of obstruction of the small intestine, and polyps causing such obstruction were usually removed surgically.

Pigmentation: In addition to our data, we shall include observations made by Japanese researchers supplementing the original documentation by Peutz (2) and by Jeghers et al (1). The pigmented lesion is composed of accumulations of flat, dark brown or black macules about the size of rice seed. Although the margin may be irregular, the lesion is usually rod-shaped, with the long dimension parallel to the ridges on the lips or the fingers (Fig 10).

The melanin spots are symmetrically distributed in specific anatomical locations including the lips or perioral region (94.1% in our series), the buccal mucosa (65.8%), and distal portion of the limbs (73.9% in the upper and 62.2% in the lower extremities), with additional spots in other locations in 21.2% of examined cases. Pigmentation is usually greater on the lower lip than on the upper; it usually occurs on the palmar or plantar surface of the terminal segment of digits, less commonly on the palms and soles.

Histologically, an accumulation of melanin pigment and an increased number of melanocytes is seen in the basal layer of the epidermis, particularly in the stratum spinosum but not in the stratum germinativum of the palmar and plantar surfaces (9).

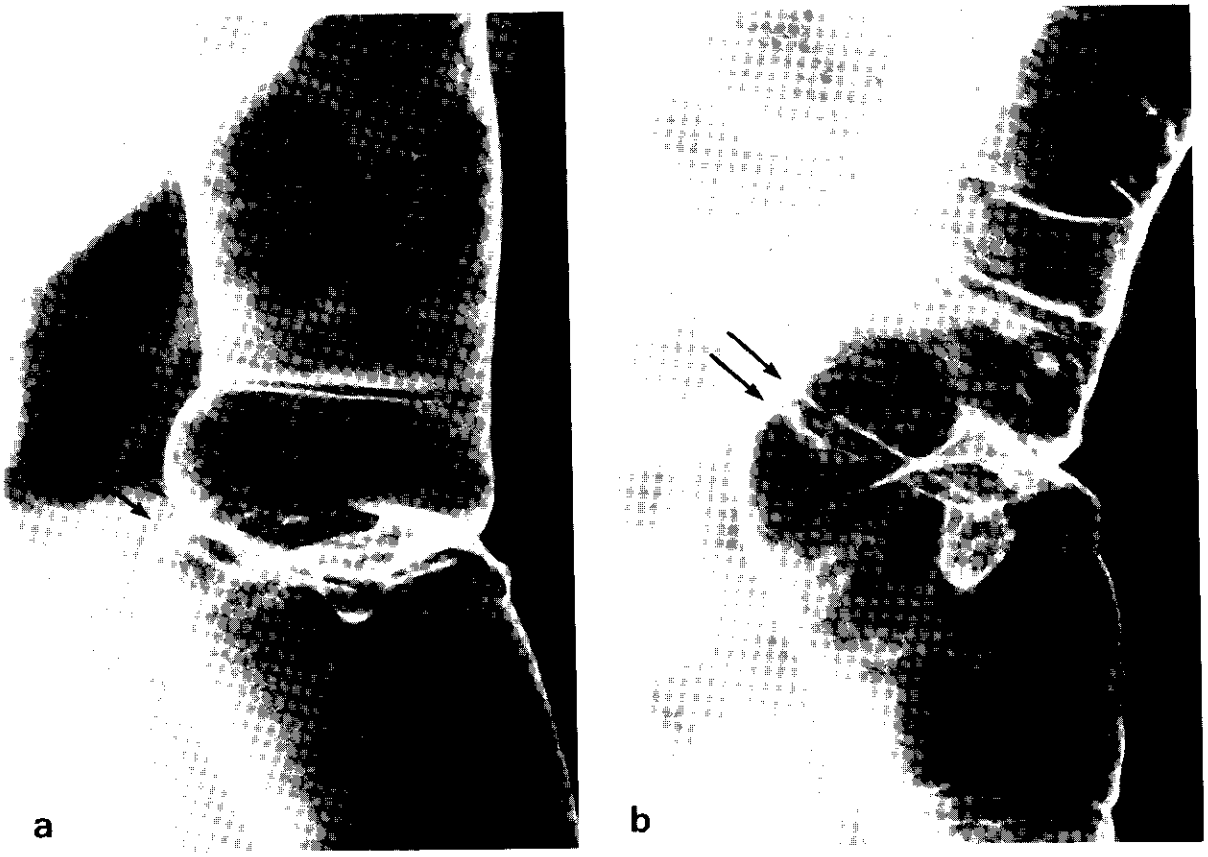

Fig 8. Barium enema x-rays of the descending colon of case P-J 21, III-2. (a) taken 9 August 1972 and (b) 19 October 1973. The double arrow indicates the site of anastomosis, performed in 1969. The single arrow indicates a small sessile polyp.

Fig 9. Microscopic view of a jejunal polyp from case P-J 19, III-7. (a) Characteristic features of P-J polyps proliferating from normal mucosal structures with heterotopic epithelial proliferation into the muscularis propria. (×7). (b) Cystic structures in the muscle layer, with appearance of mucoid carcinoma (×120).

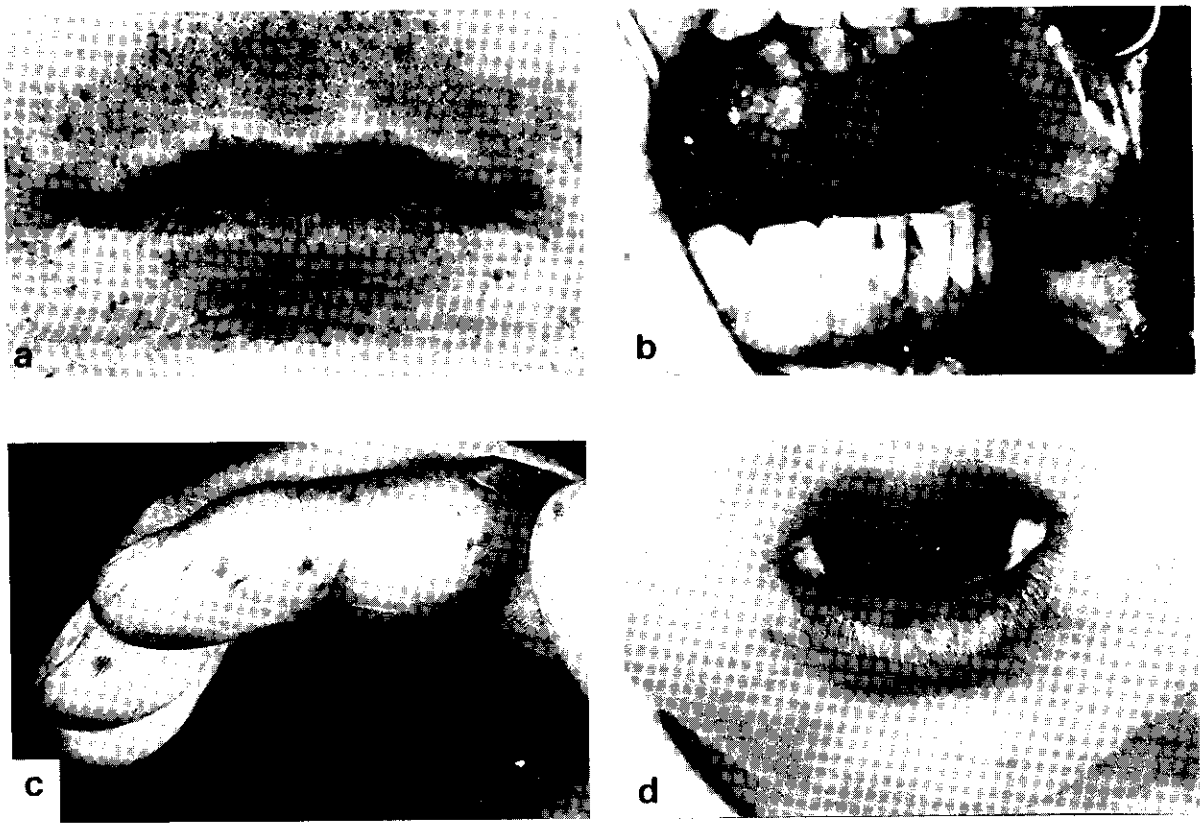

Fig 10. Melanin pigmentation. (a) Symmetric distribution of pigmentation on the lips and perioral regions of case P-J 15, III-4. (b) Pigmentation in the buccal mucosa of the same patient. (c) Pigmentation on the index finger of the right hand of the same patient. Note the arrangement of macules along the cutaneous ridges of the index finger. (d) Early pigmentation in the lower lip of P-J 15, IV-42 (4-year-old son of the patient in a, b, and c). No pigmentation was noted on his extremities.

This finding differs from that in nevus spilus (lentigo) in which the pigment is found in the stratum germinativum (10). Usually the parents first notice the appearance of pigmentation on the lower lip as a few small, solitary, dark macules when the affected child is one or two years of age. As the child grows, the number increases and the spots cover a wider area of the skin. In five patients of the present series pigmentation was not present on the lips, but occurred on other parts of the body such as the buccal mucosa or the digits. These patients were all over 45 years of age, indicating that fading of the lip pigmentation may occur with age as reported by Peutz (2). Therefore, if one examined only the lips of family members in a genetic survey it would be possible to overlook a diagnosis of the P-J syndrome in a parent of an affected child.

Survival: In our literature review, we found only 12 deaths (6.8%) in 176 reported cases. The outcome of the disease in the remaining 154 persons is not known.

Our data on the survival rate of 102 *follow-up cases* may not be statistically representative but are clinically informative. As shown in Figure 11, the slope of the curve for the P-J syndrome is not as steep as that for familial polyposis coli (6) but indicates a much shorter survival than in the normal (or control) population.

Cause of death: Of the 102 *follow-up cases*, 36 were known to have died. In each case information concerning the cause of death was obtained from hospital records or from death certificates.

Causes of death were categorized as: (1) death due to malignant neoplasm, (2) death due to complications of polyposis, including intussusception and bleeding, and (3) death due to other diseases (Table III).

Of the deaths occurring before age 30, 42.9% were due to polyposis; death occurring after age 30 was attributed to neoplastic diseases in approximately 60% of cases. Malignant diseases apparently are most responsible for the decrease in the slope of the

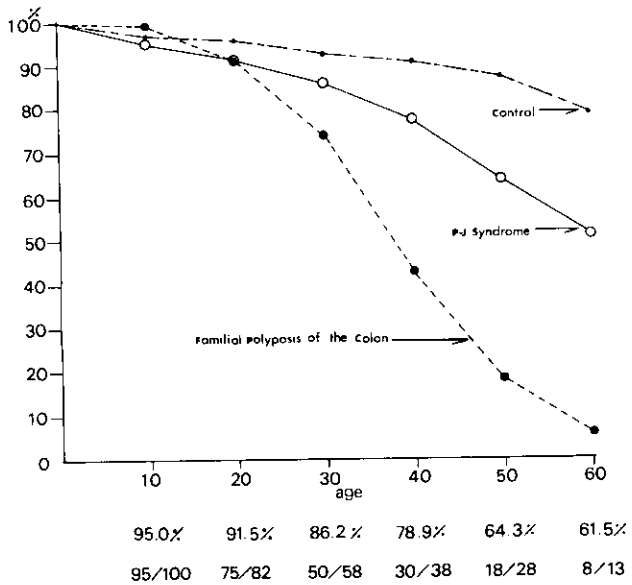

Fig 11. Survival rate of 102 *follow-up cases*.

curve for the P-J syndrome at older ages (Fig 11).

Analysis of the type of neoplastic lesion causing death in 24 patients (17 *follow-up cases* and 7 *medical literature cases*) reveals that cancer of the small intestine occurred in only two patients (one in the duodenum and one in the jejunum), but that cancer of the colon occurred in eight patients. Other sites of tumors included stomach, liver, gall bladder, pancreas, lung, uterus, ovary, and bone (Table III).

Heredity: Affected parents were found in 57 cases (25 affected fathers and 32 affected mothers). In one case we found an affected sib, but diagnosis could not be established in either parent. Therefore, the 58 so-called familial cases amounted to 45.7% of the 127 affected individuals whose family histories were ascertained.

In the *follow-up cases* 17 propositi (=A) had an affected parent. There were 50 sibs over five years of age (=B) and a total of 28 affected (including propositi) (=C), so the segregation ratio (as calculated by the formula $\frac{C-A}{B-A}$) is 0.333. No consanguinity was detected.

TABLE III

Cause of Death in 36 *Follow-Up Cases*

Cause of Death	Age Under 30		Age Over 30		Total	
1) Due to malignant neoplasms in:						
Stomach	1				1	(2)*
Duodenum	1				1	
Jejunum and ileum						(1)
Large intestine	2		5		7	(1)
Liver			1		1	
Gall bladder			1		1	
Pancreas			1		1	(1)
Lung			2		2	(1)
Uterus			1		1	
Ovary			1		1	(1)
Bone			1		1	
Subtotal	4	(28.6%)	13	(59.1%)	17	(47.2%)
2) Due to polyposis						
Intussusception	4		1		5	
Bleeding	2		1		3	
Subtotal	6	(42.9%)	2	(9.1%)	8	(22.2%)
3) Due to other diseases						
Cardiovascular			4		4	
Postoperative	1		1		2	
Acute inflammatory	2		1		3	
Tuberculosis	1				1	
Accidental			1		1	
Subtotal	4	(28.6%)	7	(31.8%)	11	(30.6%)
Grand total	14	(100.0%)	22	(100.0%)	36	(100.0%)

* Numbers in parentheses indicate data from *literature cases*.

II. Management

In general, this disease should be treated conservatively, for the patient will necessarily have many intestinal operations during his life and the risk for development of malignancy is not as great as in familial polyposis coli.

If operative measures are required, injury to instestinal mucosa should be as limited as possible, for such injury is sometimes associated with the growth of new polyps as seen in P-J 21, III-1 (Fig 8). All efforts should be made to avoid peritoneal adhesions which would complicate the inevitable later surgical procedures.

The patient should be advised to see a physician knowledgeable about P-J at regular intervals, or immediately upon the occurrence of symptoms. In Japan we are in the process of establishing a nationwide registration system for patients with polyposis that should enhance follow-up of these patients.

Small intestine: If intussusception should occur, polypectomy is mandatory, for with repeated attacks intussusception becomes more severe and at times ischemic damage necessitates intestinal resection. As seen in Table III, this is the major cause of death in younger patients.

The technique of polypectomy that we recommend is illustrated in Figure 12. After reduction of intussusception, the base of the advancing polyp is detected by a dimple produced when the intestinal wall is stretched. Through a small longitudinal incision adjacent to the dimple, the polyp is extracted and, if the dimple is large, a spindle-shaped section of wall including the base of the stalk is removed with the polyp. This maneuver removes the lesion and possible invasion of the base of the stalk, yet minimizes the defect in the intestinal wall. When polyps of considerable size are detected elsewhere in the small bowel, these can also be removed through the same opening by an "artifical intussusception technique" as seen in Figure 12d. Thus when multiple polyps are to be resected, the location of the first incision should be carefully selected in order to resect

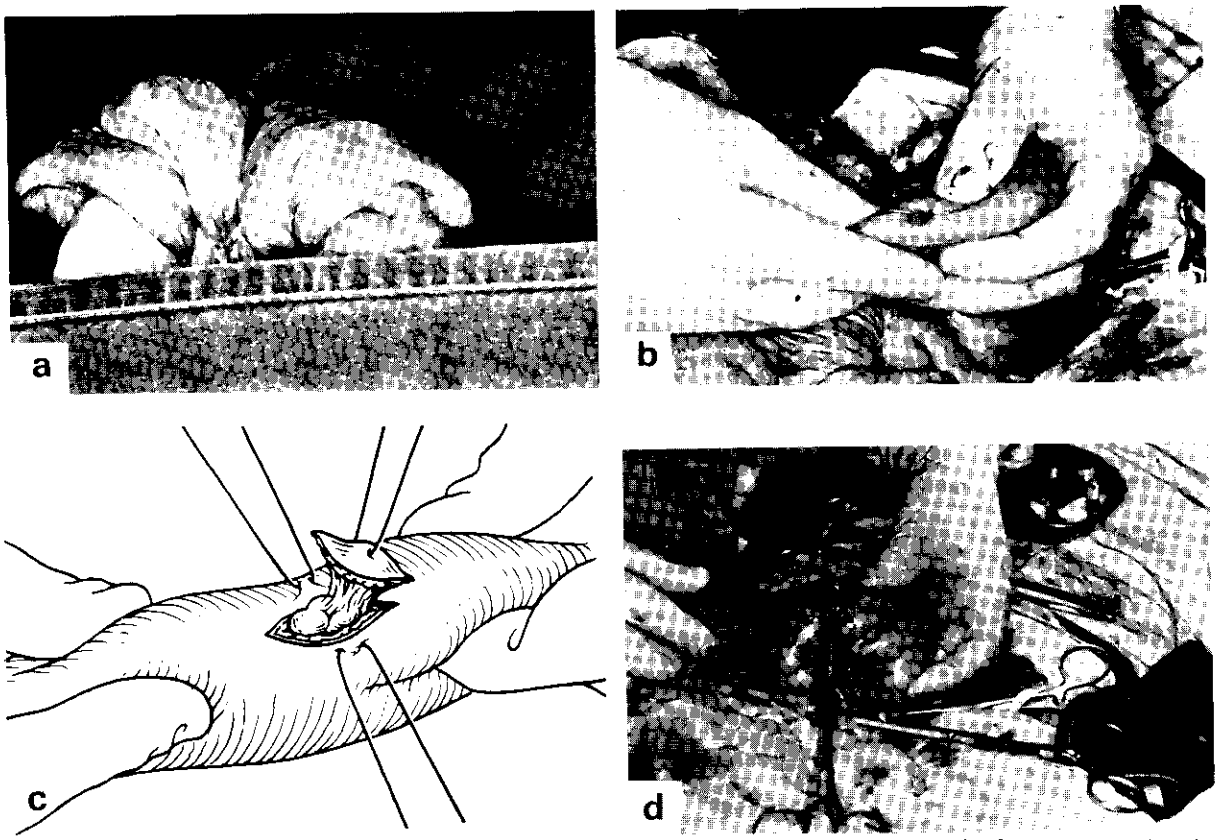

Fig 12. Operative techniques in polypectomy of the small intestine (case P-J 15, III-4). (a) Multiple intussusceptions in varying directions, seen in the jejunum and ileum. (b) A dimple indicating the presence of a polyp with a rather wide base. (c) A polyp with a wide base is being removed with part of the intestinal wall. (d) Another polyp is extracted through a single opening by the "artificial intussusception technique."

as many polyps as possible. Extensive polypectomy of small polyps by multiple incisions is of no value and could even be harmful because of the ensuing course of the disease. Segmental resection of the intestine should be avoided so far as possible to prevent malnutrition disorders as seen in P-J 19 (Fig 2) in whom less than 1 m of small bowel was left after repeated resection, and who finally died from malnutrition.

Stomach: Polyps in the stomach do not usually produce acute complications. Advanced stomach cancer was discovered in three of the *literature cases*. Because they were all teenage patients, we feel that adult patients need examinations only at yearly or biennial intervals.

Large intestine: Polyps of the large intestine rarely produce intussusception, but if a large number of polyps occur, they may cause continuous bleeding. Fiberscopic polypectomy is then useful. If the patient is more than 30 years old and the polyps are numerous, subtotal colectomy with cecoproctostomy may be the procedure of choice because of the high risk for development of cancer.

CONCLUSION

Although half a century has elapsed since the discovery of the Peutz-Jeghers syndrome, few reports have been concerned with its natural course. We have investigated this problem by analyzing all available information concerning the P-J syndrome in Japan. Our own cases number eight (which includes the first case reported in Japan), six of whom have been followed for longer than ten years; in addition, 76 cases in 72 families have been registered from other hospitals by means of nationwide surveys from 1961 to the present. A family study and follow-up survey were made and complete pedigrees were produced from family records; when this information was accumulated on 70 cases we found 32 additional affected relatives. Follow-up has been completed on 102 cases. The survival rate at 60 years of age was considerably lower for patients with the P-J syndrome for unaffected controls. Thirty-six (34.6%) were known to have died; the major cause of death in the group under age 30 was intussusception or bleeding from polyposis (43%); malignant neoplasms of various anatomical sites were the chief causes of death (60%) in the group over 30 years of age.

Cancer of the colon caused 8 of 24 deaths attributed to malignancy, and cancer of the small intestine was the cause of death in two cases. We believe that persons with the Peutz-Jeghers syndrome are at increased risk for the development of cancer, particularly of the colon.

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