Multiple Cutaneous and Subcutaneous Lesions Occurring Simultaneously with Hereditary Polyposis and Osteomatosis[1]

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THREE widely different manifestations of abnormal growth were observed in the same six members of a family group consisting of 51 individuals. Forty-four members were found to be free from all three abnormalities. One child had one of the three types of abnormal growth. The kindred first had been encountered in an investigation (Gardner, 1951) of the incidence of intestinal polyposis.

All fifty-one living members were examined by appropriate clinical methods for intestinal polyposis. In the course of these examinations "surface tumors" were also observed. These were of two types—hard and soft. Family members referred to the hard lumps as "bone tumors" in contrast to the "soft tumors" which were confined to the cutaneous and subcutaneous tissue. The "bone tumors" were investigated (Gardner and Plenk, 1952) by means of roentgenological examinations of the skull and forearms in all members of the group and the entire skeleton when warranted. Pathological studies were made from four individuals and the diagnosis of osteomatosis was established. The same six patients with intestinal polyps also had multiple osteomas. None of those free from intestinal polyps had osteomas. The pattern of inheritance (Gardner, 1951; Gardner and Plenk, 1952) for both the intestinal polyps and the osteomas was interpreted as that of a dominant gene. Either a single pleiotropic gene responsible for both manifestations, or two closely linked genes would account for the data. The nature, incidence and mode of inheritance of the "soft tumors" will be considered in this paper.

RESULTS OF EXAMINATIONS FOR "SOFT TUMORS"

Three kinds of "soft tumors" were found to be prevalent in the group. These were identified by microscopic examination as epidermoid cysts, fibromas and ill-defined masses of connective tissue. More than one type occurred in the same individuals. Some sibs had cutaneous and subcutaneous lesions while others living in the same home had none. In one family including two children,

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the father and younger daughter had multiple epidermoid cysts while the other daughter was free from such lesions. In another family the father and two of the three children had "soft tumors" while the third who was intermediate in age had none. It is probable, although demonstrated pathologically in only three, that all six individuals had connective tissue masses or fibromas.

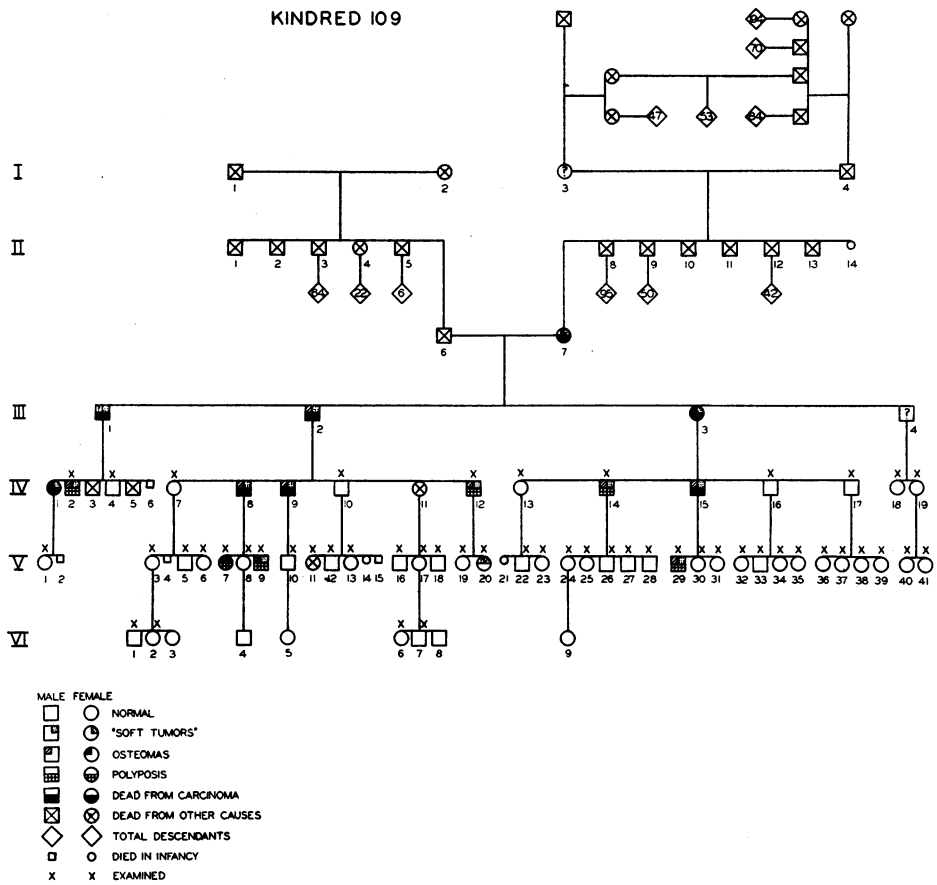

FIG. 1. Pedigree of family group showing incidence of "soft tumors," osteomas, and polyposis

The family group is represented diagrammatically in figure 1. Positive results of previous examinations for intestinal polyposis and osteomatosis as well as those for "soft tumors" are indicated on the chart. Laboratory examinations including hematocrit, stool guaiac tests, blood analysis for calcium, phosphorus, total serum protein, albumin, globulin, and alkaline phosphatase were conducted in four patients with growth abnormalities. Six individuals (IV-2, IV-12, IV-14, V-7, V-9, and V-29) were found to have multiple polyps of the colon and multiple osteomas in the skull bones. These same six patients were

observed to have multiple cutaneous and subcutaneous lesions. The case results and pertinent histories are summarized as follows:

When examined, IV-2, age 45, had on his back three lesions varying from 3 to 6 cm. in diameter. One removed from the lower mid region of the back for pathological study is illustrated in figure 2. This patient had several similar lumps on his arms, legs and head. One "soft tumor" 6 cm. in diameter was observed in the inguinal area. The patient remembered conspicuous soft lumps on different parts of his body continuously since he was about 14 years of age. Neither IV-2 nor his close relatives could be sure whether or not the growths were present in earlier childhood.

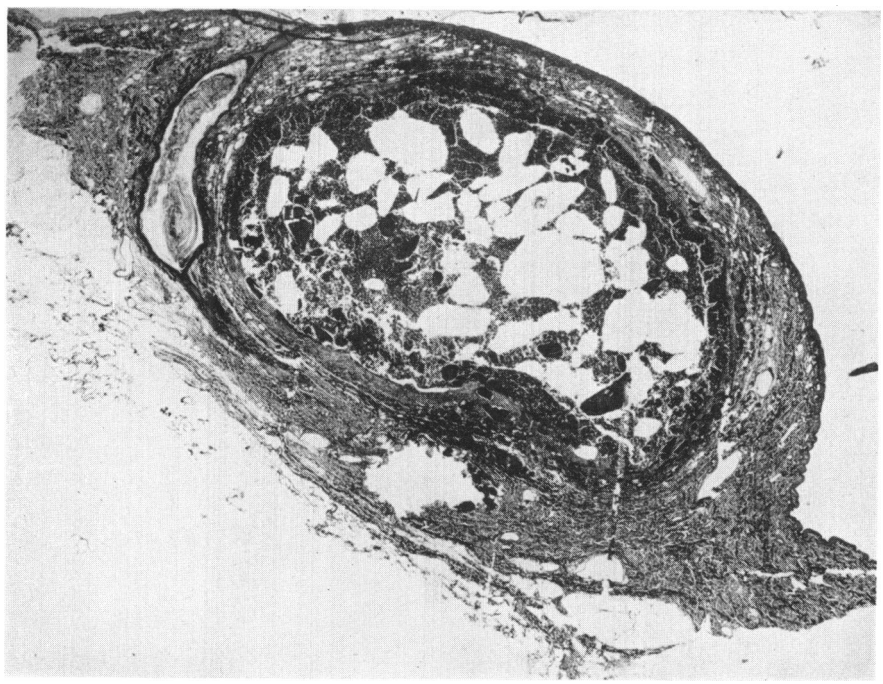

FIG. 2. Cross section of lesion removed from IV-2 in lower mid region of back

At the time of the examination IV-12, age 32, had four conspicuous lesions, on his back and one on the right shoulder (Fig. 3). Twenty-six "soft tumors," some firm and fibrous, were counted on his body. Five were resected for study and identified as epidermoid cysts. Numerous lesions, mostly epidermoid cysts but some fibrous masses, had been removed periodically over a period of years by the family physician. Seventeen had been taken from this patient at one time. Two lesions, removed from the head some years before the present examination, were described by the surgeon as leathery and fibrous in nature. They had been called fibromas although no pathological study was made.

Numerous "wens" had been observed on the body of IV-12 by his close associates from early childhood. His daughter (V-20), age 6, also had several cysts on her face and body which had persisted since early childhood. One was removed from the face of V-20 and identified as an epidermoid cyst.

IV-14, age 43, had several hard apparently fibrous masses on his body. Four were removed previously from different parts of the body including the area behind the ear, the navel, the lateral aspect of the thigh and the interscapular area. All of those removed were described as cysts. One measuring 1 cm. in

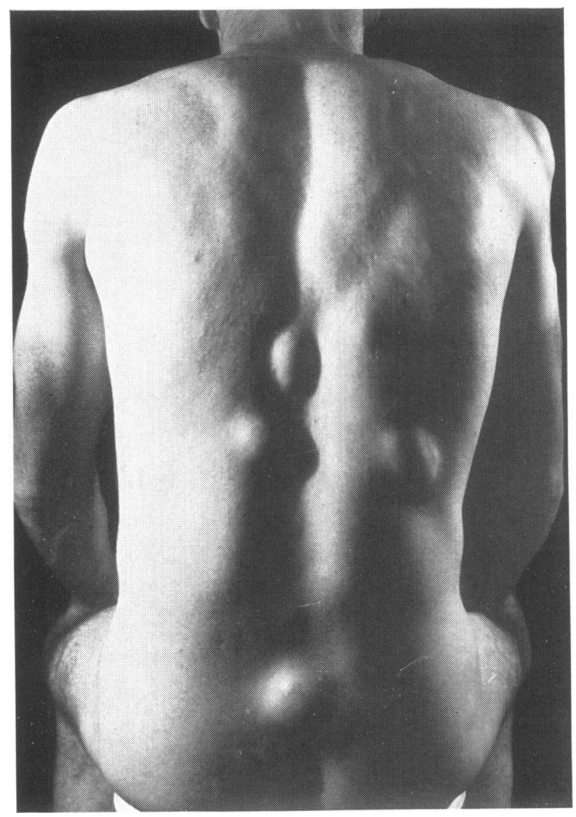

FIG. 3. Back of IV-12 showing epidermoid cysts

diameter was observed on the left eye lid at the time of the examination. In connection with a surgical procedure in 1927 for the removal of an osteoma in the frontal bone, a thick, fibrous mass was taken from the surface of the forehead. Soft irregularities were observed by IV-14 and his relatives on various parts of his body since his early youth.

When examined, V-7, age 20, had two hard fibrous lesions on her scalp and one on her forearm. A cyst had been previously removed from the side of her head. The lesion on her forearm was biopsied and identified as collagenous

and fatty tissue. The tissue was similar to that diagnosed as "fibroma" in other patients but a capsule was not present. The younger brother (V-9), age 14, of V-7 had seven firm subcutaneous masses on his head and body at the time of the examination. Most of these were on the scalp. They varied from 1 to 3 cm. in diameter. One was located on top of the left shoulder. Another was on the lateral aspect of the left forearm. A firm mass was located behind the right ear (Fig. 4). This was removed for microscopic study and identified as fibrous connective tissue, not encapsulated. The specimen measuring 3.5 x 2.4 x 1.2 cm. consisted of a leathery, almond-shaped mass of firm pearly grey tissue. The cut surface revealed slightly whorled fasciculated tissue which was

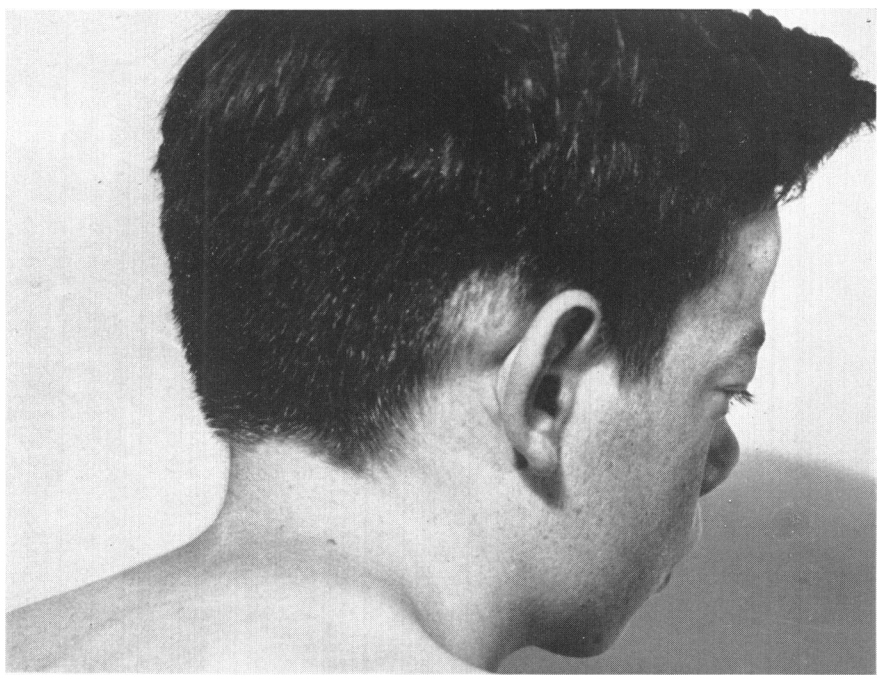

FIG. 4. Head of V-9 showing fibrous connective tissue mass behind ear

spotted yellow. Microscopic examination revealed longitudinal and cross-sectioned loose fibers which formed the bulk of the mass. Blood vessels, nerves, and foci of fat were scattered throughout. Another lesion about 1 cm. in diameter was removed from the center of the back. In the surgical procedure a smaller lesion about 0.5 cm. was also located and removed. These two specimens were diagnosed by the pathologist as "fibromas" (Fig. 5). Subcutaneous lumps had been observed on the body of V-9 by his close associates from his infancy. A projection in the medial region of the forehead of this patient at three months of age was illustrated in family photographs.

When examined, V-29, age 20, had at least two lesions on his body which,

on superficial examination, closely resembled those taken from V-7 and V-9, described above. One was located on the back of the right hand and one was below the right scapula. A similar mass had been removed from the shoulder several years earlier.

In addition to the six individuals described with intestinal polyps, osteomas, and subcutaneous lesions, one other (V-20), age 6, also had subcutaneous masses. Previous examination revealed minor bone changes of the type which may precede osteomas. No intestinal polyps were detected at proctoscopy. All

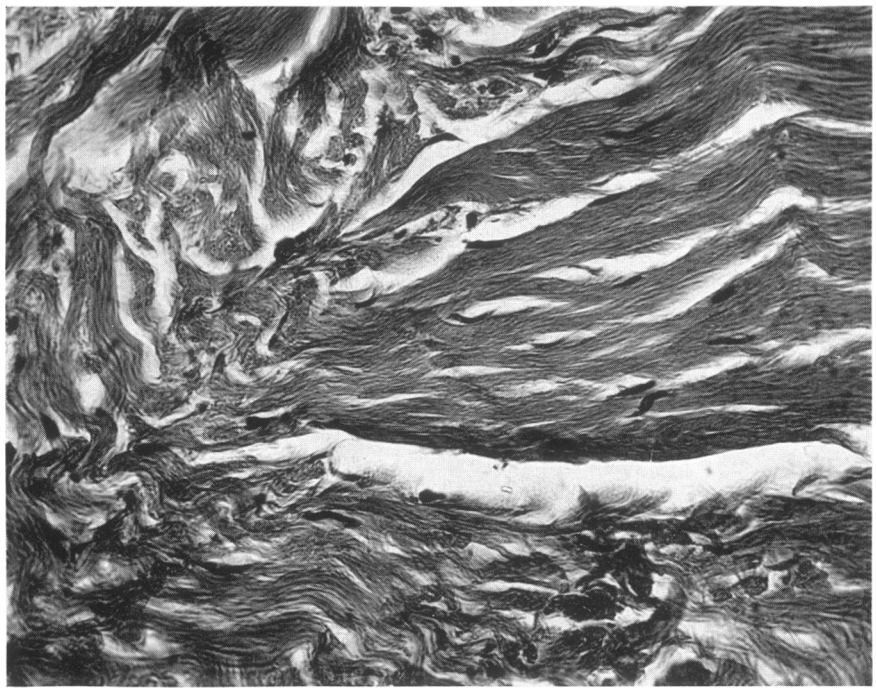

FIG. 5. Cross section of fibroma removed from V-9

other members of the group were interviewed and examined and found to be free from subcutaneous lesions of any kind. Close relatives were also interviewed and no history of such lesions was detected. Three manifestations of abnormal growth (polyposis, osteomatosis and subcutaneous lesions) were present in the same six individuals while all other members of the family group except V-20 were free from all three anomalies.

HISTORY OF DECEASED MEMBERS

All ancestral lines (Fig. 1) of the family group were studied as completely as possible. Evidence for the presence of the abnormalities discussed here was

found in only one branch of the kindred. Information concerning the deceased members of this branch is summarized in Table 1.

TABLE 1. EVIDENCE FOR INTESTINAL POLYPS, OSTEOMAS, AND SUBCUTANEOUS LESIONS AMONG THE DECEASED MEMBERS OF GROUP

INDIVIDUAL	DATE OF DEATH	AGE AT DEATH	INTESTINAL POLYPS	OSTEOMAS	SUBCUTANEOUS LESIONS	SOURCE OF INFORMATION
II–7	1909	53	Death from carcinoma of bowel	Unknown	Several	Relatives
III–1	1935	58	Colectomy performed; death from carcinoma	Unknown	Multiple	Relatives and friends
III–2	1921	41	Death from carcinoma of bowel	Hard irregularities on head	Multiple	Relatives and friends
III–3	1916	33	Death from carcinoma of rectum	Hard irregularities on head	Multiple	Relatives
III–4	1942	58	Suggested from symptomatic evidence	Unknown	Two said to have been removed	Relatives and friends
IV–1	1937	34	Positive diagnosis colectomy	Hard irregularities on head	Multiple. Two removed from back	Hospital records, relatives
IV–3	1929	22	Death from "intestinal flu"	None observed by relatives	None	Relatives
IV–5	1923	11	None. Accidental death	None observed by relatives	None	Relatives
IV–8	1940	35	Symptomatic. Death from carcinoma of rectum	Hard irregularities on head	Several. One or more removed	Relatives, photographs.
IV–9	1936	29	Positive diagnosis colectomy	Positive diagnosis and removal	Multiple cysts	Family, barber and relatives
IV–11	1941	29	None. Accidental death	None observed by relatives	None	Relatives
IV–15	1941	31	Symptomatic. Death from carcinoma of stomach and bowel obstruction	Multiple bony exostosis of scalp and forehead	Multiple	Relatives
V–11	1950	20	None	None observed	None	Examination, personal history

The oldest individual for whom definite positive evidence was available was II-7. She died in 1909 from carcinoma of the colon and was known to have "surface tumors." Her mother (I-3) had died in 1891 at the age of 64. Infor-

mation concerning the cause of her death was meager. The records in the mortuary from which she was buried recorded the cause of her death as "cancer." No death certificate or medical or hospital records were available. No one knew definitely whether or not she had "surface tumors." The descendants of I-1 and I-2 have been interviewed and examined when warranted. No polyposis, osteomatosis or "soft tumors" were detected. Likewise the descendants of I-3 by another husband and the descendants of I-4 by a second wife have been interviewed and examined. None of the three abnormalities here considered were detected.

The available evidence suggests that the same relationship between intestinal polyps, osteomas, and subcutaneous lesions observed among the living members of the group also existed in earlier generations. Eight of the thirteen deceased members were reported to have died with carcinoma of the colon and rectum. Presumably all of these individuals had multiple intestinal polyps. Pathological verification was available for two (IV-1 and IV-9). Six were reported to have had osteomas. Positive diagnosis was available for one (IV-9) of the six. Data were not available for two (II-7 and III-1). All eight who had carcinoma of the colon and presumably multiple polyposis were known to have had subcutaneous tumors or cysts.

INHERITANCE OF SUBCUTANEOUS LESIONS

The pattern (Fig. 1) of inheritance for intestinal polyposis (Gardner, 1951) and multiple osteomas (Gardner and Plenk, 1952) was characteristic of a dominant gene. Since the same individuals expressed both manifestations of abnormal growth and other members of the group were carefully examined and found to have neither abnormality, a single defective gene was postulated to account for intestinal polyps and osteomas. An alternative hypothesis would postulate separate but closely linked dominant genes for the two expressions.

The inheritance of the subcutaneous lesions was complicated by the different, apparently unrelated, kinds of abnormal surface growths occurring among the members of the group. Subcutaneous lesions were present in each individual with intestinal polyposis and osteomas. Other members of the group free from intestinal polyps and osteomas were interviewed and examined and found to be free also from subcutaneous lesions. Although different kinds of lesions occurred simultaneously, connective tissue masses probably were present (or removed) in all living individuals with subcutaneous lesions. It was difficult to visualize any connection between polyps of the colon, osteomas of the membraneous bones and subcutaneous masses. Yet the correlation in this family group was impressive and may represent more than a coincidence. Some fundamental gene-controlled process may have given rise to all three manifestations. The alternative hypothesis involving three or more closely linked genes should also be considered.

In another kindred (No. 134 in the records of the Laboratory of Human Genetics, University of Utah) intestinal polyposis has been found to follow a dominant pattern of inheritance but no osteomas nor subcutaneous lesions have been identified. Epidermoid cysts were found to follow an hereditary pattern in two other large kindreds (No. 77 and No. 184) but no cases of polyposis nor osteomas were detected. In the kindred (No. 109) under discussion these abnormal growths occurred in only one branch. Members of other branches have been interviewed, examined and found to be free from all three manifestations. If a single gene is involved it must behave differently from those genes postulated for kindred 134, 77 or 184. Either different genes or modifiers in the genetic environment may account for the different genetic action in the different kindreds. A new dominant mutation expressing itself first in I-3 or II-7 is suggested to account for the origin of the defective gene in kindred 109.

The literature includes several cases of hereditary tumors and cysts. Syndromes such as "epiloia" including different kinds of tumors along with other abnormalities have been described. None seem to fit the present case in which intestinal polyposis, osteomas and subcutaneous lesions occur simultaneously in the same individuals in one branch of a large kindred. This combination may prove valuable for control of cancer following intestinal polyposis in kindred 109. Since the bone and subcutaneous abnormalities seem to occur early in the individuals destined to become afflicted with polyposis, early diagnosis and treatment may be facilitated.

SUMMARY

Fifty-one members of a family group were examined for subcutaneous tumors and cysts. Seven were positive and forty-four were negative. Six of the positive patients were shown by previous examinations to have multiple intestinal polyps and multiple osteomas. The other was a child who also had minor bone changes but no intestinal polyps. Other members of the group were examined and found to have no intestinal polyps, osteomas, nor subcutaneous lesions. The lesions were of three kinds, epidermoid, cysts, fibromas and ill-defined masses of connective tissue. Different kinds were present in the same individuals. Fibrous connective tissue masses were probably present in all positive cases. Pathological evidence is available for three patients. A dominant mode of inheritance was interpreted for all three manifestations. A single defective gene arising from a mutation is postulated to account for the abnormalities in this family group.

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