Follow-up Study of a Family Group Exhibiting Dominant Inheritance for a Syndrome Including Intestinal Polyps, Osteomas, Fibromas and Epidermal Cysts

ELDON J. GARDNER

Utah State University, Logan, Utah

A SYNDROME including multiple or diffuse intestinal polyposis (Gardner, 1951), osteomas (Gardner and Plenk, 1952; Plenk and Gardner, 1954), fibromas and epidermal cysts (Gardner and Richards, 1953) has been investigated in a Utah family group. The most serious aspect from the standpoint of the family under consideration was the polyposis, known to predispose to carcinoma of the colon and rectum (Cripps, 1881; Dukes, 1930; Lockhart-Mummery, 1934). Eight closely related people representing three generations in this kindred (No. 109) had died of carcinoma originating in the lower digestive tract at the time (1948) the investigation was initiated. A pattern of inheritance characteristic of a single dominant gene was established for intestinal polyposis and other manifestations of the syndrome in Kindred 109 (Gardner, 1955).

The purposes of this report are: (1) to summarize the data obtained previously (1950-55) on the different manifestations, which had been studied separately, and to provide further evidence substantiating a hereditary syndrome; (2) to report the pertinent developments that occurred since 1955; and (3) to suggest the prognosis for current members of Kindred 109 and their descendants.

EXAMINATIONS FOR INTESTINAL POLYPOSIS

A study was initiated in the spring of 1948 when a premedical student in a genetics class called attention to a neighbor family in his home town that seemed to have an unusually high incidence of cancer. The family members were visited and found to be interested in having a study made, and they were cooperative in clinical investigations. Information obtained from the family and checked against all available medical and hospital records showed that eight deaths among family members had occurred from carcinoma originating in the lower digestive tract (Gardner and Stephens, 1950).

A clinic was established at a hospital in Salt Lake City in which examinations were provided for all living relatives of the deceased people (Gardner, 1951). All 51 living descendents of the woman (II-2, Fig. 1) in whom the first well-

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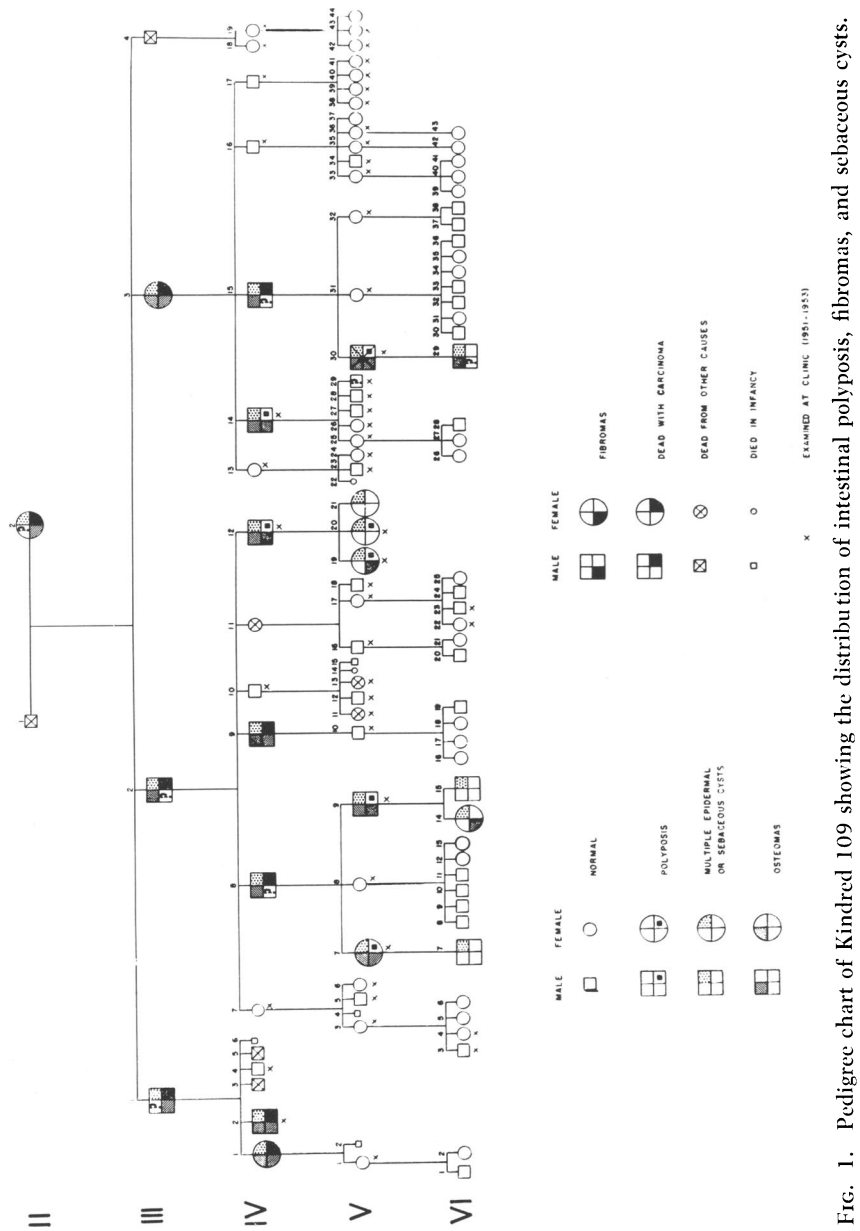

FIG. 1. Pedigree chart of Kindred 109 showing the distribution of intestinal polyposis, fibromas, and sebaceous cysts.

documented case of carcinoma had been reported were examined. Sigmoidoscopic and barium enema examinations as well as guaiac and hematocrit tests were provided. Six cases (IV-2, IV-12, IV-14, V-7, V-9 and V-30) of intestinal polyposis were detected by sigmoidoscopic observations and verified with microscopic studies of biopsied tissue and barium enema examinations. In two of the six (IV-2 and IV-14) some polyps had already developed into carcinoma. All six individuals underwent colectomies. Five recovered satisfactorily and were apparently cured from polyposis and the threat of carcinoma. One (IV-2), who was 45 years of age and had widespread carcinoma at the time of the first examination, died in 1951 from complications following the operation.

Another of the six positive cases (V-30) died at the age of 22, 3 years after his colectomy. He was admitted to the hospital with severe abdominal pain and was diagnosed as having "acute small bowel obstruction." An exploratory operation was performed, and he was found to have a large inoperable tumor of the small bowel which was diagnosed microscopically from frozen sections as a fibrosarcoma. The patient died 10 days after the operation. Hospital attendants reported that probably no direct connection existed between the polyposis or colectomy and the obstruction that took V-30 to the hospital. There may be some association, however, with other manifestations of the syndrome being considered in this study. Other investigators (Gumpel and Carballo, 1957; Fitzgerald, 1943; Miller and Sweet, 1937) have identified fibrosarcomas with what may be the same syndrome. Another case of fibrosarcoma has now been found in the family under discussion (VI-14, Fig. 1; see below).

The ages of the six individuals positive for intestinal polyposis ranged from 13 to 44 at the time of the first examination or the onset of symptoms. The youngest of the six (V-9) apparently developed polyposis during the period he was under observation. He was entirely free from polyps in the lower 29 cm. of the colon that could be observed when he was first examined with the sigmoidoscope at 13 years of age. The barium enema examination at the time, in which the entire colon was photographed, was also negative. Six months later one minute adenomatous polyp was observed and biopsied on the anterior wall 6 cm. above the anus. After another 6 months another polyp was seen in the anterior midline 11 cm. above the anus. Successive examinations at intervals of about 6 months over a 4-year period demonstrated increased numbers spreading over the entire colon and rectum. Numerous polyps were present throughout the colon when V-9 was 17 years of age. A total colectomy was performed in November 1954, when he was 18. Numerous polyps widely distributed through the colon were observed in the specimen.

Among the 51 descendants of II-2, 45 were negative for intestinal polyposis at the time (1950-53) of the examinations. In addition, a large number of other relatives of II-2 and of her husband (II-1), as well as representatives of other branches of their families, were examined at the clinic. No intestinal polyposis was found except among the descendants of II-2, who was reported to have died with carcinoma of the colon. It was therefore postulated that a mutation had occurred in II-2 or her mother (Gardner, 1955), who had died in 1891, but who was reported to have had symptoms that could have been those

of intestinal polyposis and carcinoma of the colon. A single dominant mutant gene could have been perpetuated among the descendants of II-2 who expressed the trait.

SYNDROME OF ABNORMAL LESIONS ASSOCIATED WITH POLYPOSIS

In the course of the interviews and examinations for polyposis it was observed that some individuals had growths of various kinds appearing on the surface of their bodies. The most conspicuous case was IV-2. Besides widespread intestinal polyposis, he had bilateral growths of the mandible (Fig. 4 of Plenk and Gardner, 1954). X-ray and pathologic studies showed these growths to be osteomas. Two cousins of IV-2 (IV-8 and IV-9) who had died from carcinoma of the colon were remembered by relatives and shown from family photographs to have had similar conspicuous external growths. Another cousin (IV-15), who also had died from carcinoma, was described at autopsy as having multiple bony exostoses.

The evidence for bony growths associated with multiple polyposis in family members seemed to justify a systematic survey of the entire group for bone abnormalities. Routine x-ray examinations of the skull and long bones of the arms and legs were performed for all members of the group previously examined for polyposis and for many relatives in other branches of the kindreds. Eight bones or bone groups were observed in all individuals. Bones found in the initial examination to be involved with osteomas are summarized in table 1. The

TABLE 1. BONES INVOLVED WITH OSTEOMA FORMATION IN INDIVIDUALS PREVIOUSLY KNOWN TO HAVE MULTIPLE POLYPOSIS

Individual	Bone Involvement
IV-2	Maxilla, mandible, ethmoid, sphenoid, frontal, zygoma, temporal, long bones
IV-12	Maxilla, mandible, sphenoid, frontal zygoma, temporal, long bones (diffuse cortical changes)
IV-14	Maxilla, mandible, ethmoid, frontal
V-7	Maxilla, mandible, ethmoid, sphenoid, long bones (diffuse cortical changes)
V-9	Maxilla, ethmoid, long bones (diffuse cortical changes)
V-30	Maxilla, sphenoid

same six individuals found previously to have intestinal polyposis were shown to have osteomas associated with some of the bones examined. All other members except two young girls, V-19 and V-20, ages 11 and 7 respectively, were normal. Minor cortical changes, which according to the x-ray report may or may not be associated with osteoma formation, were observed in the long bones of the forearms of V-19 and V-20. At that time (1951) the girls did not have intestinal polyposis, but their father (IV-12) had polyposis and osteomatosis. Both girls now have intestinal polyposis and other manifestations of the syndrome.

Other unusual types of lesions which family members called "soft tumors" were also observed on the bodies of individuals with intestinal polyposis and osteomas. Several were removed from IV-2 and were identified by pathologists as trichoepitheliomas and sebaceous cysts. Other more firm lesions, which were considered by the surgeon to be connective tissue masses, were left to be removed later, but the patient died before the study could be completed.

Several lesions removed from IV-12 were classified as epidermal and sebaceous cysts. Other more firm lesions were removed from the forehead of IV-12 and identified superficially as fibromas, but were not studied microscopically. One of the children (V-19) of IV-12 had several firm lumps on her skull and back that were observed by a surgeon and identified tentatively as fibromas; she also had sebaceous cysts. The other daughter (V-20) of IV-12 had numerous cysts on her face and body. Several were removed and classified by pathologists as epidermal cysts.

Sebaceous cysts were also observed on the face and body of IV-14. His family physician had previously removed a lesion which he identified as a connective tissue mass without pathologic verification. Several lesions were removed from V-7 and identified pathologically as collagenous and connective tissue masses. Lesions taken from V-9, brother of V-7, were classed as fibromas.

Several lumps observed on the body of V-30 at the time of the first examination were considered as probable fibromas. Pathologic studies of the surface

TABLE 2. RESULTS OF EXAMINATIONS FOR INTESTINAL POLYPOSIS, OSTEOMAS, FIBROMAS, OR CONNECTIVE TISSUE MASSES AND EPIDERMAL OR SEBACEOUS CYSTS IN EIGHT MEMBERS OF THE KINDRED. ALL OTHERS WERE NEGATIVE FOR ALL FOUR MANIFESTATIONS AT THE TIME OF EXAMINATIONS (1950-53).

Individual	Age when Examined	Intestinal Polyposis	Osteomas	Fibromas or Connective Tissue Masses	Epidermal or Sebaceous Cysts
IV-2	44	Positive	Positive	Probable connective tissue masses not removed	Trichoepitheliomas and sebaceous cysts
IV-12	35	Positive	Positive	Two probable fibromas removed	Epidermal and sebaceous
IV-14	44	Positive	Positive	Connective tissue mass removed	Sebaceous
V-7	19	Positive	Positive	Collagenous and fat tissue masses removed	Sebaceous
V-9	13-17	Positive	Positive	Fibromas	Sebaceous
V-19	11	Negative	Minor cortical changes in long bones	Probable fibromas not removed	Sebaceous
V-20	7	Negative	Minor cortical changes in long bones	None observed	Numerous epidermal
V-30	19	Positive	Positive	Probable fibromas not removed	Epidermal lesions; type unknown

lesions on the body of V-30 were not made, but before he died some of these were identified tentatively as fibromas and others as epidermal lesions.

The results of observations and examinations (1950-53) for intestinal polyposis, osteomas, fibromas or connective tissue masses and epidermal or sebaceous cysts in eight members of the kindred are summarized in table 2. All examinations performed at this time on other members of the kindred were negative for all four of the manifestations of abnormal growth.

NEW DEVELOPMENTS

In April 1961, IV-12 had a colostomy. Eleven years earlier, in March 1950, he underwent a colectomy, but at that time the rectum was left in place. During the intervening years it was necessary for him to visit his surgeon every month for a checkup. New polyps were observed in the rectum and removed by cautery during almost every one of these visits. In January, 1961, a large polyp was observed, and in the next three months it grew larger in spite of the cautery treatment. Microscopic study of the biopsied polyp showed that it had become malignant. The rectum was removed and a colostomy performed.

Epidermal cysts are still large and conspicuous on the arms, legs, and trunk of IV-12. Periodically he has the largest and most troublesome cysts removed. Four small epidermal cysts removed at one time were described in the pathologic report as ovoid, yellow-white, moderately firm masses with smooth external surfaces except for attached fibrous tissue. Microscopic study showed the cysts to be lined with epidermis and to contain keratin.

Significant developments among the children of family members expressing the syndrome are summarized in table 3 and will be described in the order in which those examined are represented in Fig. 1. The oldest daughter of IV-12, (V-19) now (1962) 22 years of age, has had several polyps removed from her colon and rectum. The first polyp was observed when she was 14 years of age. The second daughter, (V-20) now age 18, also has intestinal polyposis. The youngest sister, V-21, now 8 years old, has conspicuous epidermal cysts. Her parents say that she has had them since she was born. Our clinician examined her at 19 months of age and reported a conspicuous soft lump on the side of the head in front of the right temple. It was about an inch in diameter and raised a quarter of an inch or more above the surface of the head. It felt soft and was moveable. Her parents said that this particular lump had not changed appreciably since she was 6 months of age. Another abnormality in the occipital region was hard and was identified tentatively as a fibroma. She had several other unidentified lumps on her back and shoulders.

The five children of IV-14 (V-25 to V-29) and three grandchildren (IV-26 to VI-28) all appear to be well. The youngest (V-29), age 3 when first examined (1950), had a lump on his forehead that was described in the x-ray report as: "a slight irregular protuberance in the region of the forehead about 3 cm. above the root of the nose." At age 15 the lump is still present on the forehead but no other conspicuous irregularities can be observed. He has not been examined for intestinal polyposis since he was 3 years old.

V-7 had a colectomy in June, 1951, but the rectum was left intact. She

TABLE 3. FINDINGS DETECTED AMONG THE CHILDREN OF PARENTS WHO HAVE EXPRESSED THE TRAITS OF THE SYNDROME. NO OTHER FAMILY MEMBERS EXCEPT THOSE IDENTIFIED IN FIG. 1 AND TABLE 2 ARE KNOWN TO HAVE ANY OF THESE MANIFESTATIONS.

Individual	Age in Years	Intestinal Polyposis	Osteomas, Fibromas or Connective Tissue Masses	Epidermal or Sebaceous Cysts
V-19	22	Positive	2 probable fibromas removed	Sebaceous
V-20	18	Positive	None observed	Numerous epidermal
V-21	8	Negative	Probable fibroma	Numerous epidermal
V-29	15	Negative at age 3 Not examined since	Irregular protuberance on forehead	None observed
VI-7	1	Not examined	Probable connective tissue masses	Epidermal lesions type unknown
VI-14	2	Not examined	Diffuse fibromatosis and fibrosarcoma of muscle facia and subcutaneous tissue	Epidermal lesions type unknown
VI-15	1	Not examined	None observed	Epidermal lesions type unknown
VI-29	7	Not examined	Connective tissue masses not yet excised for study	Epidermal lesions type unknown

visits her surgeon regularly for a checkup and for the removal of new polyps developing in the rectum. Several health problems that may or may not be related to the syndrome under discussion have plagued her during the past 10 years. After 11 miscarriages she had succeeded in carrying a child for 7 months when a bowel obstruction necessitated an emergency operation. The surgery was successful, and the fetus was retained. A few weeks later the baby boy VI-7 was taken by cesarean section. VI-7, now (1962) less than one year old, appears healthy but has epidermal cysts on his head and body. On the basis of family history and the presence of epidermal cysts, VI-7 has inherited the syndrome expressed in his mother and other relatives.

In August 1955, V-9 was again carefully examined at our clinic. New x-ray films of the skull showed an osteoma not previously observed involving the frontal sinuses. It measured 4.5 x 2.5 cm. in greatest diameter, completely obliterated the right frontal sinus, and extended across the midline to involve the medial portion of the left sinus. No other conspicuous changes were observed in the cranial vault. Connective tissue masses previously observed on the arms and back of V-9 had enlarged significantly by 1955. A fibroma located in the same place and similar to but perhaps larger than that removed in 1951 (Gardner and Richards, 1953; Fig. 4) was removed. A growth, sebaceous in nature, was observed on the eyelid. The examining surgeon observed that the cyst extended through the cartilage plate and could be seen on the under side of the lid. It was identified tentatively as a chalazion. In 1957, V-9 had an

osteoma removed from the orbit, and he now (1962) complains of pain in the same area.

VI-14, daughter of V-9, was born June 14, 1959, and was described as "perfectly normal" by the attending physician. As soon as the mother was home from the hospital with the new daughter she observed a small "lump" in the middle of the baby's back a short distance to the right of the spinal column. By January, 1960, the "lump" had grown to the size of a "pullet's egg" and the family physician recommended surgery. On March 4 the growth was removed and the diagnosis reported was "muscular neuropathy." The pathologist characterized the tissues as presenting a "very odd' microscopic picture. A second pathologist described the excised lesion as "diffuse fibromatosis."

In early August, 1960, another growth was observed on VI-14, a short distance to the right of the position from which the first had been removed. Most of the new growth was within the surgical scar from the removal of the earlier lesion. By the summer of 1961 the new growth had become larger than the first was when it was excised. The new growth was removed in June 1961. A large amount of connective tissue, parts of the 10th and 11th ribs and the entire 12 rib were removed. The pathologic report was, "fibrosarcoma of muscle facia and subcutaneous tissue—low grade malignancy." This histologic pattern of the tissue was distinctly different from that of the earlier lesion. Excised material was in the form of solid masses of extremely dense collagenous tissue, infiltrating the surrounding skeletal muscle and invading adipose tissue. The word "fibrosarcoma" was used to indicate a well differentiated, non-metastasizing lesion capable of progressive growth and was used synonymously with "aggressive fibromatosis." This tumor could fit in the category of desmoid tumors. This lesion may not be related to the syndrome represented in other members of this family, but two (IV-14 and V-30) of the 20 individuals (living and dead) who have expressed the syndrome have now been diagnosed as having fibrosarcoma. Also, there are cases in the literature in which fibrosarcoma has been associated with a syndrome that is presumably the same as the one under discussion. Nonmetastasizing fibrosarcoma in this syndrome may be more than a coincidence, and it will be studied further.

In addition to the sarcoma for which VI-14 has been treated, she has other abnormal growths more like those observed on her father and other family members. She now has what appear to be epithelial cysts on the top of her left foot, center forehead and left temple. There are also irregularities on her skull similar to those of her father. It is too early to excise these irregularities and to make a more accurate diagnosis. Her younger brother, VI-15, born in February 1961, also has irregularities on his head and body. Some are in the epidermis, but it is too early to be more precise concerning their nature.

VI-29, son of V-30, born November 13, 1954, one month after his father died, was first examined by our clinician at 7 months of age. X-rays of the skull and photographs of the head and body were taken at that time. At least two abnormal growths were observed in the head region: a hard projection from the occipital bone and a firm lump on the side of the head. Another abnormal mass was observed in the lower part of the back, resembling superficially the "soft

tumors" in other family members. The mother reported observing a lump in the lumbar region on top of the baby's spine shortly after his birth. When the baby was 6 months of age his mother noticed a "soft lump" in front of the left ear. At 7 years of age VI-29 still had the lesions that were recognized earlier and several more. The most conspicuous new ones were behind one ear, on the head, and on the side of the face. Some were hard, resembling the fibromas observed in other members of the family. None have yet been excised for pathological study.

DENTAL ASPECT OF SYNDROME

Fader, Kline, Spatz and Zabrow (1962) have associated multiple impacted supernumerary and permanent teeth with a syndrome that may be the same as that represented in Kindred 109. Six cases were reported by these authors as having various manifestations of the same syndrome, but intestinal polyposis has not been observed thus far in any of these patients. In our study no particular attention was given to the teeth, but the routine survey of family members by means of x-ray films and the detailed family histories have suggested several deformities of the teeth and jaws. Members of the kindred having other manifestations of the syndrome also have very poor teeth, and most who are 20 years old or older have false teeth.

IV-2, now deceased, reported in the original interview that he had had poor teeth and sinus trouble all his life. The x-ray report (Salt Lake General Hospital 6492-50, 1951) of his skull is quoted as follows: "Innumerable bony dense tumors arise from the bony structures of the skull and particularly of the facial bones as well as the mandible. The bony structure of the maxilla is grossly abnormal. The normal trabeculation is obliterated and irregular dense bone formation is seen throughout. Some of these tumors seem to project into the nasal pharynx from the posterior wall of the maxilla."

IV-8, already deceased when the study began in 1948, had false teeth before he was 22 years of age. His brother, IV-9, also deceased in 1948, was only 17 when his permanent teeth were removed. Masses of supernumerary teeth were reported to have been taken from his jaw when the teeth were extracted.

IV-12 had mentioned poor teeth in connection with the medical history taken early in this study. His routine x-ray examination, like that provided for other family members, was not particularly concerned with the teeth, but a passing observation was made in the x-ray report (Salt Lake General Hospital 4882-51, 1951) as follows: "Irregular islands of bone density are scattered throughout the mandible as well as the maxilla. This is in addition to and has no relation with a few of the root fragments which still remain in the mandible as well as one completely unerupted inverted tooth in the region of the symphysis. Some obliteration of the normal trabecular structure is associated with these findings. Irregular islands of increased bone density are also seen, scattered throughout the skull."

The three daughters of IV-12 (V-19, V-20, V-21) have had continuous trouble with their teeth. Both parents commented on the dental problems of their children in the first interviews and in those that have followed. They

spoke of these matters as if they were associated with the "soft tumors" which they had observed on all of these children since they were babies.

The routine x-ray report of IV-14 when he was 44 years of age noted that the canine teeth of the upper jaw and also the third molars had remained unerupted. In checking out the previous history of IV-14, a report was found at the Holy Cross Hospital in Salt Lake City of an admission in 1927 when the patient was 19 years old. The diagnosis was: "osteoma and follicular odontoma, unerupted teeth." Two teeth were extracted and several dentigerous cysts were removed from the region near the roots of the teeth. A large bony tumor was removed from the roof of the mouth.

V-7 had false teeth at 19 years of age. The following is quoted from the x-ray report (Salt Lake General Hospital 5769-50, 1951). "Bizarre bone changes resulting in thickening of the bone and loss of the normal trabecular substance involve particularly the maxilla as well as the greater wing of the right sphenoid. In addition to this, numerous round bony tumor masses are seen to arise from several areas in the frontal bone, from the maxilla, and from the sphenoid. The most striking involvement is of the palate with irregular thickening which seems to protrude into the antrum and into the mouth. Some of these tumors arise from the posterior wall and appear to project into the zygomatic fossa. Both jaws are completely edentulous which is certainly unusual for a patient of 21. The trabecular structure of the mandible is somewhat obliterated." Relatives who knew IV-8, the father of V-7, stated that the father and daughter had similar dental problems. As stated above, IV-8 had false teeth when he was 22 years of age.

V-9, the younger brother of V-7 and son of IV-8, has had continuous tooth trouble while under observation in connection with the present study. When he was 18 years of age two teeth were removed by the family dentist, and the dentist advised that all of his teeth should be extracted. The orthodontist, who was not acquainted with the condition in the family, said that he had only seen one other patient in his entire professional career that had a condition of the teeth and jaws like that of V-9. According to his comment the teeth were completely embedded in the bone. His curiosity led him to check in his file for the name of the previous patient with a similar condition, and it turned out to be V-19 (described above), a cousin of V-9.

DISCUSSION

The pattern of simple dominant inheritance has been well established for multiple polyposis of the large intestine (Dukes, 1952, 1958; Reed and Neel, 1955). Polyposis of the small intestine is apparently a separate disease, but has been found to follow the same inheritance pattern (Jeghers, McKusick and Katz, 1949, and others). The tendency for intestinal polyps, particularly those in the colon and rectum, to become malignant and thus to predispose to generalized cancer has been well established (Helwig, 1947, and others). Because of the importance of early detection and treatment of cancer or factors that predispose to cancer, polyps of the large bowel have become increasingly significant in the cancer control program. Polyps of the small bowel may also become malig-

nant, but their tendency to cause bowel obstruction is of more immediate clinical significance than is their tendency to predispose to cancer.

Polyposis is a rare disease in the general population, but in certain families it is extremely important (Reed and Neel, 1955). Nine of 16 deceased members of Kindred 109 died with carcinoma of the digestive tract and presumably had intestinal polyposis. The dominant inheritance pattern aids in detecting those families and family members in which polyposis is likely to occur. Other traits have been found to accompany and in some cases to precede the development of polyps. When visible or otherwise detectable traits can be associated with polyposis, additional diagnostic tools thereby become available.

Of more fundamental significance is the value of such traits in fostering a broader understanding of the basic disturbance or abnormality that precedes the occurrence of the polyps. Presumably all hereditary phenotypes have a chemical basis. More complete understanding of the manifestations may suggest underlying causes or steps between genes and traits.

A beginning in the analysis of dermatoses associated with malignant internal tumors in general was made by Curth (1955). Perhaps the most fundamental association that has been established to date with intestinal polyposis is a cytoplasmic inclusion containing deoxyribose nucleic acid (DNA) reported by Leuchtenberger (1954). The possibility of a virus associated with the disease is being considered and will be investigated as soon as another colon specimen is available.

When members of Kindred 109 were first examined in 1950 for intestinal polyposis there was no reason to expect that other types of abnormal growths would be associated with this condition. Indeed, all 51 descendants of II-2 (Fig. 1) and many relatives were transported to the clinic in Salt Lake City and examined just for polyps before the clinicians could be persuaded to check for other abnormalities. The conspicuous tumors on IV-2, IV-12, and V-9 were mentioned casually but considered to be coincidental with respect to the polyposis. A year later (1951), when the correlations had become obvious to the author, the family members were brought back to the clinic for studies of the bones, connective tissues and skin. Since that time several cases of similar associations have been reported by other investigators.

Oldfield (1954) of Leeds, England, reported a case in which multiple intestinal polyposis of the colon was associated with cutaneous cysts. O'Brien and Wels (1955) cited six cases in which benign fibrous tumors occurred simultaneously with hereditary adenomas of the colon and rectum. Weiner and Cooper (1956) reported a study in which three brothers had multiple polyposis of the colon, osteomatosis, and soft-tissue tumors. A fourth brother in the same sibship had multiple polyposis of the colon and osteomas. Gumpel and Carballo (1956) added three cases of familial adenomatosis with which fibromas, exostosis, and epidermoid cysts were detected. In addition to these manifestations, fibrosarcoma and leiomyoma were also associated with the syndrome. In all three cases the other manifestations were established prior to the detection of familial adenomatosis or to the appearance of gastrointestinal symptoms. Laberge, Saur and Mayo (1958) observed one case in which a lipoma and a

soft-tissue tumor of the mesentery were associated with polyposis of the colon. One other single case (Lazar, Crow and Brogdon, 1958) included multiple polyposis of the large bowel, osteomas, and skin tumors.

Smith (1958) reviewed the records of 201 patients with multiple polyposis and found that 17 exhibited one or more of the abnormalities included in the syndrome. Six of the 17 had desmoid tumors associated with their abdominal incisional scars. Epidermoid cysts were found in 12 and osteomas in eight of the 17 patients reported upon. Following the custom of naming a syndrome after the person first to adequately describe it, Smith identified the syndrome under discussion as Gardner's syndrome and others (Fader *et al.* 1962) have followed this lead.

Three earlier reports may have been dealing with the same syndrome. Devic and Bussy (1912) reported a single case of diffuse polyposis of the small and large bowel, associated with osteomas, fibro-lipomas and sebaceous cysts. McKittrick, Mallory, and Talbott (1935) also reported a single case including diffuse polyposis of the small and large bowel, multiple osteomata, epidermoid cysts and a history of prior excision of a fibroma or fibrosarcoma of the chest wall. No hereditary implications were drawn from these isolated cases. The third instance was the case mentioned previously of Miller and Sweet (1937) involving multiple polyposis of the small and large bowel with postoperative appearance of a "desmoid type fibrosarcoma" in the surgical scar. Three families were cited in which polyposis and carcinoma followed a familial pattern. Cases referred to in all three reports involved the small as well as the large intestine, whereas the polyposis presently under consideration is apparently restricted to the large intestine.

Two cases of intestinal polyposis (Gottesman and Perla, 1930) with other possible manifestations of the syndrome were also reported prior to the present studies. The first case included multiple fibromata of the small and large intestine, and the second involved multiple adenomatous polyps of the large intestine with malignancy. No surface tumors were reported and no hereditary aspect was in evidence. Thoma (1936) reported a case of multiple osteomas in an 18 year old male. Prior history indicated that a fibroma had been excised from the cheek of this patient. No mention was made of intestinal polyposis or epidermal cysts.

A case involving polyposis and osteomas has recently been detected in a patient who has no known connection with Kindred 109. The patient, 63 years old, was admitted to a Salt Lake hospital for treatment of a kidney condition. His medical history showed that he had suffered from intestinal polyposis and had undergone a complete colectomy at the age of 50. He had complained of rectal bleeding, diarrhea and general ill health before that operation. On general physical examination, three conspicuous nodules were observed on the head of the patient. These were diagnosed by x-ray examination as osteomas.

A sister of the patient had had multiple intestinal polyposis and had died with rectal carcinoma in 1942 at the age of 47. She had undergone a colectomy 2 years before. A brother of the patient died in 1945, when he was about 50 years old, with carcinoma of the descending colon and metastases to other or-

gans. The father had died at about 50 years of age from an unknown cause. Although the exact diagnosis of polyposis among the relatives of the patient was made only in the case of the sister, it was a probable predisposing factor for carcinoma in the brother and could have occurred in the father. The patient has no children. He has two living sisters, both beyond 70 years of age. There are 11 nieces and nephews, but none are available for examination at the present time.

The observations concerning teeth in Kindred 109 were not made as systematically and objectively as were those concerning the other aspects of the problem. Data available in the histories of the individual family members have been cited to indicate that the dental aspects reported by Fader *et al.* (1962) might indeed be a part of the syndrome under discussion. No attempt has been made as yet to determine whether the anomalies detected in the family members expressing the syndrome were present in other family members. When osteomas and epidermal cysts were investigated, all family members (51 at that time) were given the same examination, and the results were treated objectively. It would be of great interest now to study objectively the dental aspects in this family group and to determine whether the tooth and jaw anomalies are confined to the people expressing the syndrome.

Even though the expressions of the different abnormal growths in Kindred 109 seem unrelated, one basic chemical reaction controlled by a single gene could possibly influence several apparently unrelated tumors. Johnson (1953) has presented a theory for the common origin of certain tumors including osteomas and fibromas.

Another Utah family (Kindred 134, Gardner and Woolf, 1952), being investigated at the same time as Kindred 109, included eight cases of intestinal polyposis, all of which were among the descendants of a particular woman. The pattern of dominant inheritance was observed, but in this family no other kinds of tumors were detected. In still another Utah family (Kindred 133), occasional discrete polyps of the colon and rectum may be inherited (Woolf, Richards and Gardner, 1955). No other kinds of tumors were detected in the members of this family who had polyps of the colon.

SUMMARY

A follow-up and recheck has been made of members of a family group in which a syndrome including multiple polyposis of the large intestine, osteomatosis, fibromatosis, and epidermal and sebaceous cysts has been expressed. The general results followed the patterns previously reported, and several new aspects were observed.

Two cases classified as fibrosarcoma have been added to the list of manifestations in people who evidence other aspects of the syndrome.

A man with multiple polyposis, osteomas, fibromas, and epidermal and sebaceous cysts had two daughters who had other manifestations of the syndrome when the last report was made. These girls now (at ages 22 and 18, respectively) have multiple polyposis.

Five young children of patients expressing the syndrome now have epidermal cysts and/or fibromas.

Recent data support the earlier description of the syndrome and confirm a pattern of inheritance that is dependent on a single dominant gene. Among the children who lived long enough to be identified as having or not having the syndrome and who had one parent who expressed the syndrome, 20 were positive and 16 were negative. This observation is not significantly different from the 1:1 ratio expected in cases of single gene dominant inheritance.

A dental anomaly, recently associated by Fader *et al.* (1962) with a syndrome that could be the same as the one under discussion, also may be present in Kindred 109.

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