The Nevoid Basal Cell Carcinoma Syndrome

DAVID E. ANDERSON,[1]* WILLIAM B. TAYLOR,[2]
HAROLD F. FALLS,[1,3] AND RUTH T. DAVIDSON[1]

[1]Department of Human Genetics,
[2]Department of Dermatology,
[3]Department of Ophthalmology,
The University of Michigan Medical School,
Ann Arbor, Michigan 48104.

THE NEVOID BASAL CELL CARCINOMA SYNDROME (Fig. 1) is a genetic entity recognized in its fullest expression by multiple nevoid basal cell carcinomas (nevoid is used in the context of a developmental or congenital anomaly), cysts of the jaws, a variety of skeletal anomalies, ectopic calcification, and a pitting of the skin of the palms and soles (Howell and Caro, 1959; Ward, 1960; Gorlin and Goltz, 1960; Anderson *et al.*, 1964; Clendenning *et al.*, 1964; Maddox *et al.*, 1964; Pollard and New, 1964; Anderson and Cook, 1966). A hypophosphaturic response to parathyroid hormone with or without brachymetacarpalism has also been associated with the syndrome as has medulloblastoma (Clendenning *et al.*, 1964; Gorlin *et al.*, 1965).

The syndrome has received relatively little genetic attention. This is surprising on two counts: (1) The entity is apparently more frequent than was originally suspected, as evidenced by the hundred or so cases appearing in the literature since 1959; and (2) the entity is a hereditary form of basal cell carcinoma. The present report thus summarizes some genetic aspects of the syndrome in 13 kindreds and also provides an indication of the extent to which the syndrome varies both within and among kindreds.

CLINICAL MATERIAL

The 13 propositi who form the basis of the present report were ascertained through the University Hospital of the University of Michigan. Dermatologic, ophthalmologic, and radiologic examinations were performed on fifty members of the kindreds. Medical records for evaluating syndrome status were available on an additional 12 individuals. Among the entire examined and documented group, 34, including the propositi, were found to have features of the syndrome. One kindred (8585) was not examined, but basal cell carcinomas and/or jaw cysts were verified through medical records. This kindred is not included in the summary of clinical findings (Table 1) but is included in the genetic anal-

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*Present address: Section of Human Genetics, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77025.

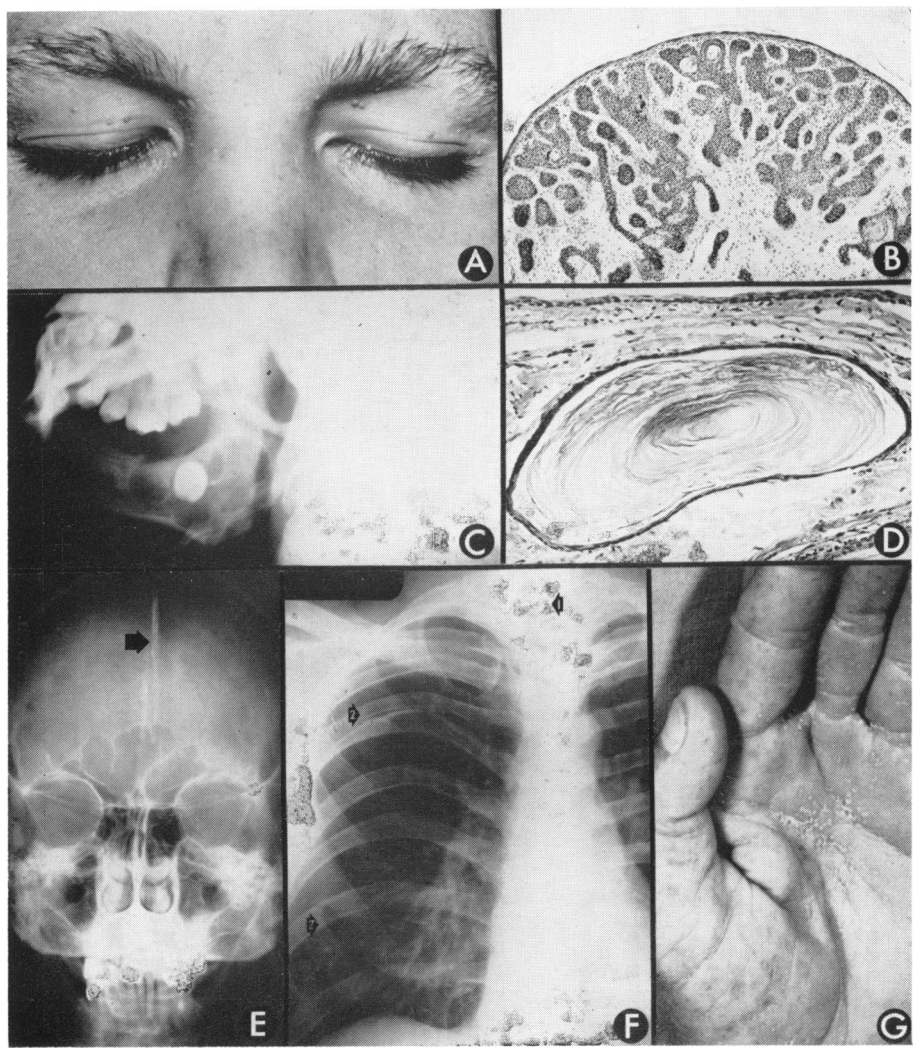

FIG. 1. Major components of the nevoid basal cell carcinoma syndrome. A. Nevoid basal cell carcinomas around the eyes of a young boy. These may ultimately become invasive in adulthood. B. Section through nevoid basal cell carcinoma showing anastomosing narrow strands of basal cells. C. Multilocular cyst associated with a molar. D. Section through a multilocular cyst showing squamous cell lining of a cyst at extreme top and lower right hand corner and a microcyst in the connective tissue. E. Lamellar calcification in the falx cerebri. F. Skeletal anomalies including (1) spina bifida at D-1 and (2) bifurcation of the second and fifth ribs and scoliosis or curvature of the spine. G. Pitting of the skin of the palm and fingers. (Fig. 1 A and B, courtesy of Dr. J. B. Howell.)

ysis (Table 2). Metabolic studies for evaluating a hypophosphaturic response to parathyroid hormone were not performed nor were examinations for brachymetacarpalism.

A complete summary of the clinical findings in each kindred is too lengthy for inclusion here and will be reported elsewhere. However, a clinical summary

TABLE 1. SUMMARY OF CLINICAL FINDINGS IN INDIVIDUALS WITH THE NEVOID BASAL CELL CARCINOMA SYNDROME*

Kindred number	Pedigree number†	Age	Basal cell lesions	Pits of palms	Jaw cysts	Ectopic calcification	Skeletal Anomalies				Ocular findings
							Sella	Spine	Ribs	Hands-feet	
1166	II-1	32	+++++	?	++++	++	?	?	?	?	None
8994	II-3	34	+++	0	++++	+++	+	+++	+++	+	Chalazia
9049	II-3	18	+	0	+++	+	+	++	++	0	Exotropia
9086	II-1	45	0	+	+++	++++	0	++	+++++	+	Hypertelorism
	III-1	27	0	0	+	+	0	0	+	0	None
	III-5	11	0	0	++	++	+	0	++	0	Hypertelorism
	III-7	8	0	0	0	0	+	+++	++	0	Hypertelorism
	III-8	7	0	0	0	0	+	+++	+++++	0	Exotropia, hypertelorism
	III-3	5	0	0	0	0	?	++	+++++	0	Unknown
9133	II-2	17	0	0	++++	+	0	0	+++	0	Exotropia, nystagmus
9139	III-6	44	+++++	0	+	++	0	0	+	0	Exotropia
	IV-14	25	+++++	?	++++	++	0	0	0	0	None
	IV-15	21	+++++	+	+	0	0	0	0	0	None
	IV-17	17	+++++	+	++++	+	+	+	0	0	None
	III-7	40	+	0	+++	++	+	+	+	0	None
	IV-21	17	+++++	+	++++	++	0	0	0	+	Coloboma
	IV-22	15	+++++	+	++++	+	0	0	0	+	None
	IV-10	20	0	0	++	?	?	?	?	0	None
	II-5	72	++++	?	?	+	?	+	++	0	None
9153	II-3	41	+++++	+	+++	+++	+	+++	++++	+	Chalazia
	I-1	79	++++	+	+++	?	?	?	?	+	Absence of cornea
9287	II-4	33	+++	+	+	+	+	0	0	+	Exotropia
9288	II-6	60	+++	+	0	++	0	0	++	0	Exotropia
9289	I-1	37	++++	0	+	++	+	+	0	0	Exotropia, amblyopia
	II-2	9	+	0	0	+	+	+++	0	0	Exotropia, nystagmus
	II-3	5	0	0	0	0	+	++	+++++	0	None
9462	II-13	15	++++	+	+++	+++	+	0	0	+	None
9642	II-1	61	++++	+	0	+	+	+++	+++	0	Exophoria

*A question mark (?) indicates that the status of this lesion or anomaly is unknown.
†The propositus is opposite the kindred number.

of one kindred is provided to illustrate the types of lesions and anomalies usually encountered in affected adults and children.

Kindred 9289

The propositus (I-1) was a 37-year-old, married, Caucasian male, who was ascertained through a referral from Dermatology. He presented with approximately 300–500 basal cell carcinomas on the face, trunk, and extremities. The lesions had been repeatedly diagnosed as basal cell carcinomas since age 24. Sebaceous cysts were also noted on the body. There was no pitting of the skin of the palms or soles. Ophthalmologic examination disclosed left amblyopia, exotropia, medullated nerve fibers, and carcinoma of the eyelids. Frontal bossing and a wide skull were also evident. Radiograms disclosed a large cyst in the right mandible, marked lamellar calcification in the falx cerebri and tentorium cerebelli, bridging of the sella turcica, and spina bifida of the first dorsal vertebra. His nine-year-old daughter (II-2) had a nevoid basal cell carcinoma on the right shoulder confirmed by histologic study, ectopic calcification in the falx, bridging of the sella turcica, complete fusion of the upper cervical and incomplete fusion of the lower cervical vertebrae, and scoliosis. Ophthalmologic examinations revealed facial and skull asymmetry, hypertelorism, exotropia of the right eye and ptosis and nystagmus of the left eye. His five-year-old son (II-3) manifested megalocephaly with frontal bossing, unusual hair growth over the bridge of the nose; Sprengel's deformity; bilaterally deformed, fused, and bifid ribs; spina bifida of the seventh cervical vertebra; hemivertebra of the fourth dorsal; and bridging of the sella turcica. A 12-year-old son of the propositus was not affected.

RESULTS

Clinical Features

The only component observed in affected individuals in other kindreds but not in Kindred 9289 (Table 1) was pitting of the skin of the palms and soles (Fig. 1) and skeletal anomalies of the hands and feet, mainly in the form of syndactyly or polydactyly. Multiple and recurring basal cell carcinomas were the presenting complaint in the propositus of Kindred 9289 as well as five other propositi. These lesions were first recognized at an average age of 19 years. In the remaining seven propositi, the presenting complaint was referable to multiple and recurring cysts of the jaws, which first developed at an average age of 15 years. The clinical features of the components that characterize the syndrome have been adequately summarized in recent reviews and need not be repeated (Clendenning *et al.*, 1964; Howell *et al.*, 1964; and Gorlin *et al.*, 1965). The microscopic features were summarized by Maddox *et al.* (1964), Mason *et al.* (1965), and Graham *et al.* (1965). The clinical, pathologic, genetic, and therapeutic aspects of the syndrome were recently summarized at a clinical conference (see Clendenning, 1966).

Some new components were observed in the present series and deserve brief comment since they occurred at sufficiently high frequencies to indicate an association with the syndrome. For example, bridging of the sella turcica

should obviously be added to the spectrum of skeletal anomalies, since it was observed in 14 of 23 individuals in the syndrome group and in 3 of 27 in the unaffected relatives who were similarly examined. This difference, as shown by adjusted chi square, is highly significant ($P < .01$). Its frequency in the general population is approximately 7% (Hueblein, 1946). With regard to anomalies of the hands and feet, polydactyly was observed in 3 of 27 and syndactyly in 5 of 27 individuals in the syndrome group; neither was observed in 27 examined and unaffected relatives. These frequencies are larger than expected on the basis of population frequencies. Polydactyly has a frequency of 4 to 7 per 10,000 live births in Caucasians and 40 to 50 per 10,000 in Negroes, and syndactyly (the major form) a frequency of 2 to 25 per 10,000 in both races, according to Gorlin and Pindborg (1964). Although polydactyly, syndactyly, and bridging of the sella turcica may well be associated with the syndrome, they are too nonspecific in themselves to be diagnostic. However, in the presence of one or more of the major components, they may be useful in identifying the syndrome.

Ophthalmologic problems were also frequent in the present series and should be added to the syndrome complex. The most common problems were exotropia (strabismus) and exophoria, as evidenced by their presence in 9 of 27 individuals in the syndrome group and none of 28 in the examined unaffected group. This difference is highly significant ($P < .01$). A complete discussion of the ophthalmologic problems will be presented elsewhere by one of the authors (H. F. F.).

Expressivity

The various components were subjectively scored to reflect multiplicity or the extent of involvement. Basal cell lesions were scored from 0 to 5 according to the number of lesions. Pitting of the skin of the palms and soles was scored merely as to its presence or absence. Jaw cysts were scored from 0 to 4 according to the number of jaw quadrants in which cysts developed. A count of the individual cysts was attempted but was abandoned after encountering difficulties in distinguishing between recurrent and *de novo* cysts and between adjacent unilocular and multilocular cysts. The score for calcification is the number of structures containing ectopic calcification. The score for skeletal anomalies is a count of the individual defects of the sella turcica, ribs, spine, hands, and feet.

Table 1 clearly demonstrates variability in expressivity, which appears to be more pronounced among than within kindreds. Kindred 9139, for example, is characterized by extensive cutaneous involvement and a low frequency of skeletal anomalies, averaging about one anomaly per individual. However, in Kindred 9086, a Negro kindred, biopsies to date have not revealed nevoid basal cell carcinomas, and most individuals have a variety of skeletal anomalies of the skull, ribs, and spine averaging about six per individual. There is little or no question that the syndrome was present in this kindred and in the 45-year-old proposita, because she manifested several characteristic features, including pitting of the skin of the palms, which are considered pathognomonic

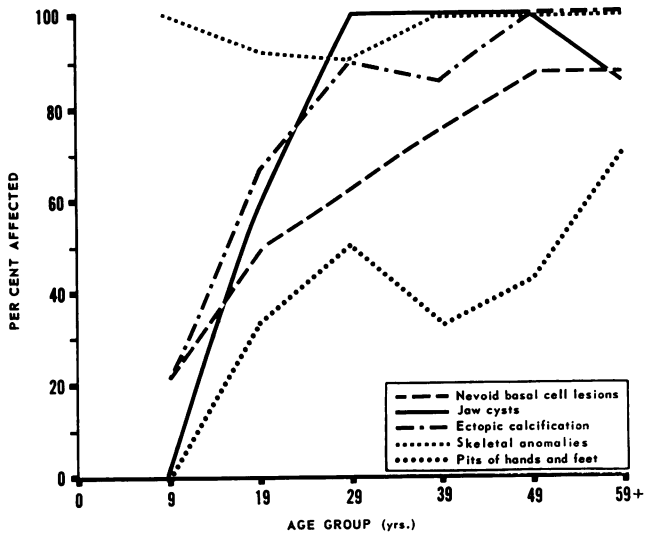

FIG. 2. Age-specific affection rates of the major components of the nevoid basal cell carcinoma syndrome according to a moving average of two successive age classes after nine years of age (to provide larger numbers per class and smoother curves). Propositi are included in their respective classes, since age was not a factor in ascertainment and the purpose here is only to show age effects on the major components.

(J. B. Howell, personal communication). The syndrome and the nevoid basal cell lesions have been described previously in a Negro (Nichols and Solomon, 1965). Thus, the adults in this kindred appear to manifest minimal expression of the cutaneous component but full expression of the other components.

No important differences in expressivity or frequency of the disease are observed between males and females. Age, however, does have an important influence on expressivity (Fig. 2). Nevoid basal cell lesions show a definite increase in frequency with age as does pitting, but the increases are at slower rates than those shown for jaw cysts and ectopic calcification. In fact, these two components are more fully and completely expressed at younger ages than either cutaneous lesion. Conversely, skeletal anomalies with frequencies between 85% and 100% show no increase with age, which is to be expected since these are congenital.

Genetic Features

The pedigrees (Fig. 3) clearly point to a dominant mode of inheritance in eight of the 13 pedigrees, but the five sporadic cases are more difficult to explain. They may represent mutations or phenocopies or may be merely the consequence of incomplete examinations of the kindreds. In fact, the examination rate among sibs of sporadic cases was 40%, and none of the sporadics had children, while the examination rate among sibs and children of familial cases was 70%. It is conceivable, therefore, that some cases appear to be sporadic owing to a lowered probability of detection of the syndrome in their respective kindreds.

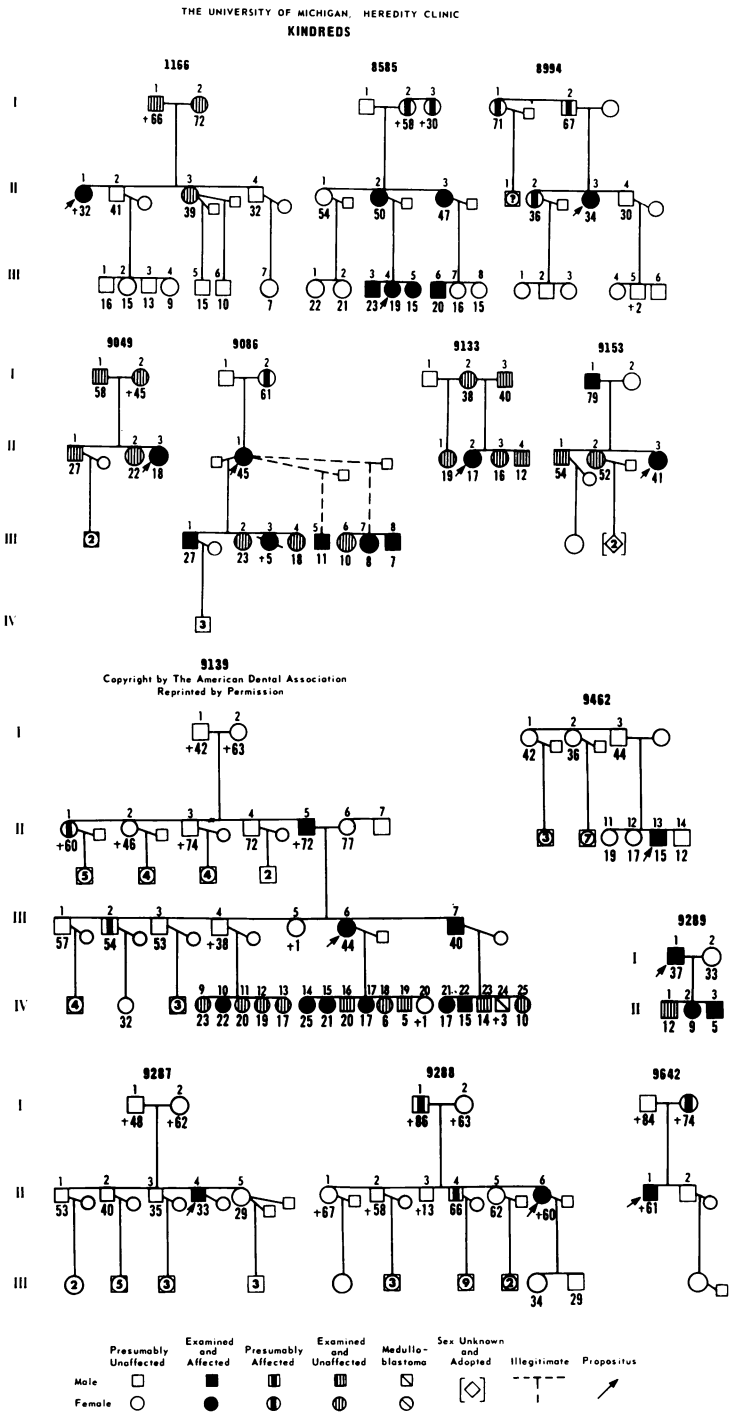

FIG. 3. Summary of pedigrees with the nevoid basal cell carcinoma syndrome.

TABLE 2. FREQUENCY OF AFFECTED AND UNAFFECTED INDIVIDUALS IN SIBSHIPS ACCORDING TO SEX AND SOURCE OF INFORMATION

Type of sibship*	Number of sibships	Affected		Unaffected	
		Male	Female	Male	Female
Examined sibships:					
Affected father	4	2	3	4	6
Affected mother	3	4	6	2	4
Partially examined sibships:					
Affected father	3	4	1	5	2
Affected mother	3	1	2	1	3
Reported sibships:					
Parental status unknown	3	2	4	2	1
Totals	16	13	16	14	16

*The propositus was excluded from the sibship.

For sibships at risk, the frequencies of affected males compared with unaffected males and of affected females compared with unaffected females are not markedly different from the expected 1:1 ratios (Table 2). The same is true for total males and females, thus ruling out an abnormal sex ratio and differential viability between sexes.

Sex linkage can also be ruled out by the similarity of results for affected fathers and affected mothers and the occurrence of affected males from affected fathers. In the absence of differences, the results for affected fathers and mothers and the two sexes were combined, providing a total of 15 affected and 16 unaffected children in the completely examined sibships, a result which agrees closely with the 1:1 ratio expected under the null hypothesis of dominance. The totals for partially examined and reported sibships are 8 affected and 11 unaffected, and 6 affected and 3 unaffected, respectively. Each of these likewise agrees with a 1:1 ratio, as does the total of 29 affected and 30 unaffected children.

The closeness of the observed to expected number of affected individuals points to a penetrance estimate of 97% in the examined sibships and 98% for all of the sibships at risk. Kindred 9139 contains the only instance of incomplete penetrance where an apparently unaffected individual (III-4) had an affected parent and an affected child. This individual was not known to be affected when he died at age 38 of coronary arteriosclerosis. If he had survived to an older age, detectable lesions might have developed, or lesions may have been present before death but were minimally expressed and therefore not detected. Either of these is possible since two of his brothers and a daughter have minimal expression of the syndrome.

DISCUSSION

The nevoid basal cell carcinoma syndrome should be suspected when nevoid basal cell lesions, particularly if they are multiple and have an early age at

onset, are observed in association with one or more of the following: cysts of the jaws, pitting of the skin of the palms and soles, ectopic lamellar calcification in the falx cerebri, and developmental anomalies of the skull, spine, ribs, and extremities. The syndrome should also be suspected in patients with jaw cysts in association with the preceding components. Other features which may be helpful in diagnosis include a large skull, parietal and frontal bossing, hypertelorism, broad nasal root, exotropia, and a positive family history of multiple skin cancers and/or jaw cysts.

These components may occur in various combinations, and some individuals may not always manifest the nevoid basal cell carcinomas and/or the jaw cysts at the time of examination (Table 1). Some of the variability in clinical expression is undoubtedly the consequence of an age effect, as evidenced by the frequencies of the nevoid basal cell lesions, pitting of the skin of the palms and soles, jaw cysts, and ectopic calcification increasing at different rates with an increase in age (Fig. 2). Skeletal anomalies, however, are not age-dependent. That they are not influenced by age but yet vary in frequency (and type) among kindreds, as shown by kindred 9086 and 9139, points strongly to genetic and environmental influences modifying the expression of the syndrome over and above the age effects. This may also apply to the age at onset and multiplicity of the nevoid skin lesions. Kindred 9139 had an average age at first recognition of seven years and is further characterized by an extreme multiplicity of lesions averaging 3,000 per affected adult (Anderson and Cook, 1966). Another well-documented kindred, previously reported by Anderson *et al.* (1964), had an average age at first recognition of 14 years and in adults lesions numbering in the hundreds. These two kindreds also differ in the frequency and type of their skeletal anomalies, and both differ from kindred 9086 in regard to skeletal and cutaneous involvement. The clinical picture, therefore, appears to be characteristic of a kindred. Whether this is a consequence of a modifying gene(s), environmental influences, or different alleles at the primary locus is unknown.

The present genetic findings indicating dominant inheritance are in agreement with those noted earlier by Anderson *et al.* (1964), Rasmussen (1963), Schønning and Visfeldt (1964), and Gerber (1965). Meerkotter and Shear (1964) suggested recessive inheritance to explain one affected individual from consanguineous parents, but the possibility of dominance is not excluded, particularly in the absence of detailed examinations of the parents. Gorlin and Goltz (1960) originally suggested dominant inheritance but with low penetrance. However, the present study, as well as those by Anderson *et al.* (1964) and Gerber (1965), shows that detailed examinations of family members will demonstrate a highly penetrant gene. None of the previous studies has detected significant differences in affection rates between males and females, and all have shown male to male transmission, thus pointing to autosomal inheritance. This finding is contrary to the proposal of sex linkage by Clendenning *et al.* (1964). The birth order of individuals in sibships segregating for the syndrome showed no significant departure from randomness in the earlier study of Anderson *et al.* (1964).

Chromosome studies have revealed no significant changes in number or structure. Yunis and Gorlin (1963) did observe an unusually long arm of one of the chromosomes no. 1, but this was likely of no significance, since the abnormality occurred independently of the syndrome in one family and was not found in another family in which the syndrome was segregating.

On the basis of these results, the syndrome can be regarded as a hereditary type of basal cell carcinoma with a dominant mode of inheritance and determined by a highly penetrant autosomal gene with multiple and variable effects. The syndrome should thus be added to the list of other kinds of cancer or potentially cancerous conditions, such as Gardner's syndrome, Peutz-Jeghers's syndrome, polyposis coli, retinoblastoma, xeroderma pigmentosum, and multiple neurofibromatosis, which likewise have genetic bases and are inherited in a simple Mendelian manner.

SUMMARY

Thirteen propositi with the nevoid basal cell carcinoma syndrome were ascertained from patients of the University Hospital of the University of Michigan. Examinations were conducted on 50 family members, and medical records were available for evaluating the syndrome status on 12 additional members. The major clinical findings in 28 examined and medically documented individuals affected with the syndrome are summarized.

The expressivity of the syndrome was highly variable, and more variable among than within kindreds. Some of the variability in expressivity was attributable to age effects and some to genetic and/or environmental influences. The syndrome in eight of the pedigrees, as in other reported pedigrees, was inherited in a dominant manner. It was concluded that the syndrome refers to a hereditary form of basal cell carcinoma with a dominant mode of inheritance and is determined by a highly penetrant autosomal gene with multiple and variable effects.

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