Genetic Services At A Center for Craniofacial Anomalies

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Provision of genetic evaluation and counseling as part of the routine service of a cleft palate team is an evolving concept. This paper reviews relevant advances in clinical genetics and their impact on craniofacial centers. The patient population, diagnostic categories, and service delivery model at one such center, not necessarily representative, are analyzed to demonstrate that genetic services are now essential.

KEY WORDS: genetics, genetic counseling, craniofacial

Introduction

Analysis of the NIDR Directory on Cleft Palate Team Services for 1969-70 showed that only 3% (4/138) of cleft palate teams in the U.S. included a clinical geneticist (USHEW, 1970). The figure increased to 26% (31/117) in 1976 (Table 1), when 55% (65/117) of U.S. cleft palate teams reported access to special genetic services such as chromosome analysis, biochemical testing, and dermatoglyphics. Of 132 world-wide cleft palate teams reporting, 59% (78/132) provided clinical and/or special genetic services (USHEW, 1976). The trend toward increased availability of genetic services for patients with facial clefts has continued.

The membership application of the American Cleft Palate Association does not specifically refer to genetics, although numerous other disciplines are identified. The report of the Conference to Identify Objectives of the Cleft Lip/Palate Treatment Team (Morris et al., 1978) suggested inclusion of a geneticist as a member of the ideal team but was not specific in defining this role, an omission also noted by Jorgenson et al. (Jorgenson 1978).

It is our view that genetic services are an essential rather than an elective component of a comprehensive program designed to meet the needs of patients and families with cleft lip/palate and other craniofacial anomalies. To support this view we offer the record of the Center for Craniofacial Anomalies at the University of Illinois (CCFA-IL). We realize that the diagnostic profile of our case flow may be skewed toward the complex and is, therefore, not necessarily representative of other cleft palate centers. Only as individual comparisons are made with this report will common denominators of need for clinical genetic services emerge.

Growth of Clinical Genetics

Many factors have contributed to the increased interest in clinical genetics. They include: (1) advances in cytogenetics, biochemistry, microbiology, and syndrome identification; (2) application of these advances to clinical medicine; (3) development of professional training programs and formal organizations; and (4) increasing public awareness of and demand for genetic services.

At this writing, it is inconceivable that a birth defects center could function without access to genetic diagnostic and counseling

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This investigation was supported in part by grants from the National Institutes of Health (DE 02872) and Maternal and Child Health Services, Department of Health and Human Services.

TABLE 1. Genetic Services Available in Cleft Palate-Craniofacial Centers, 1976* (N = 132)

Country (# Centers Reporting)	*Column A Clinical Personnel Only*	*Column B Special Diagnostic Tests Only*	*Column C Clinical Personnel and Special Diagnostic Tests*	*Column D Total With Clinical Personnel (Columns A + C)*	*Column E Total With Special Diagnostic Tests (Columns B + C)*	*Column F Total With Genetic Services (Columns A + B + C)*
U.S.A. (n = 117)	4 (3%)	38 (32%)	27 (23%)	31 (26%)	65 (55%)	69/117 (58%)
Canada (n = 3)	0	1	2	2	3	3/3 (100%)
Other (n = 12)	1	3	2	3	5	6/12 (50%)
Totals	5 (4%)	42 (32%)	31 (23%)	36 (27%)	73 (55%)	78/132 (59%)

* Cleft Palate Team Directory, 1976.

services. Often, geneticists constitute the core staff in such centers. In contrast, many cleft palate and craniofacial programs, whose origins antedated birth defects centers and the discipline of clinical genetics, lag in their ability to provide genetic information. One reason may be that many advances in genetic knowledge and technology have limited applicability to craniofacial disorders.

For example, while numerous chromosomal disorders have associated craniofacial anomalies (Gorlin et al., 1976; Cohen, 1978), the majority of patients with craniofacial anomalies do not have chromosomal disorders. In addition, although primary biochemical errors may someday be found to explain craniofacial anomalies, such errors have not been identified in most of the patients who gravitate to craniofacial centers. Principles of cytogenetics and biochemical genetics have been applied to early second trimester amniocentesis, a prenatal diagnostic procedure currently not useful for most craniofacial disorders. Other methods of prenatal diagnosis such as fetoscopy and ultrasonography currently have limited use in the detection of craniofacial anomalies.

The field of craniofacial anomalies has relied on the development of a third area of clinical genetics syndrome delineation. The addition of genetic services to cleft palate programs in the late 1960's followed the growth of knowledge in this field. Investigators rely on classical techniques of descriptive studies, population studies, and pedigree analysis. Several singular contributions have provided direction to this field.

Fogh-Andersen (1942) postulated the genetic independence of isolated cleft palate and isolated cleft lip with or without cleft palate. By 1976, Gorlin had identified and delineated a large number of syndromes associated with cleft lip and/or palate and distinguished them etiologically from nonsyndromic facial clefts. The etiology of syndromes associated with clefts may reside in chromosomal aberrations, single gene mutations, teratogens, or unknown causes and appear to be distinct from the more common isolated clefts of the lip and/or palate. Although there is some disagreement (Melnick, 1976), most investigators believe these latter types of facial clefts are best explained by the multifactorial model (Fraser, 1976). The theory of continuously distributed developmental variables was proposed by Galton, the father of biometry, and provides the basis for the multifactorial/threshold model. In concept, the developmental threshold separates the population into those with an abnormality and those without it. Sensitivity to environmental and genetic differences may influence penetrance and expressivity. The multifactorial/threshold model is now invoked to explain large numbers of congenital malformations, including many craniofacial anomalies.

Formalization of Clinical Genetics

Both Federal and private sources provided support for: (1) genetic services to children with congenital malformations; (2) research and research training in genetics; and (3) scientific conferences on congenital malformations. (Table 2)

As the scope of the problem of genetic diseases was recognized, and as demand for genetic services grew, innovative approaches were developed to train personnel. In 1969

Sarah Lawrence College initiated the first of many programs leading to master's degrees in genetic counseling (Marks, 1976). In recent years, court decisions have also accelerated the concern for genetic services. In a 1978 decision, the Appellate Court of the State of New York held physicians liable for the lifetime cost of care of a child with a birth defect when the physician could have advised the parents of the genetic risk in advance of the pregnancy or in time for prenatal diagnosis but failed to do so (Park v. Chessin).

Over the years, a number of professional and scientific societies have been formed in the United States to meet the needs of a growing cadre of geneticists and to sponsor annual conferences and publications (Table 3). The American Cleft Palate Association appointed its first section editor in genetics to the *Cleft Palate Journal* in 1975.

Impact of Genetics on Craniofacial Anomalies

How has increasing knowledge of the etiology and delineation of syndromes been disseminated among practitioners concerned with craniofacial anomalies? There are at least two useful measures. (1) An indirect measure is derived from analysis of publications in selected journals. (2) More directly, an index is provided by the number of cleft palate centers including genetic services (Table I). Three journals were selected for review: *Plastic and Reconstructive Surgery* (PRS); *Journal of Speech and Hearing Disorders* (JSHD); and *Cleft Palate Journal* (CPJ). No dental journal was evaluated because dentists with interests in craniofacial anomalies usually tend to publish in non-dental journals. The results of this survey are summarized in Table 4. The majority of articles dealt with syndromes and

TABLE 2. Selected Events in Formalization of Clinical Genetics

Event	*Public Support*	*Private Support*
Service	1935 Social Security Act Crippled Children's Programs 1978: National Genetics Disease Act 1st federal funding of genetic services (Rollnick, 1979)	1938: 1st U.S. Cleft Palate Clinic, Lancaster, PA 1960's: National Foundation March of Dimes birth defects centers 1st CCFA: 1967
Research	1958: NIH financial support (NIGMS, NIDR)*	1958: National Foundation March of Dimes financial support
Scientific Conferences	1959: Gatlinburg Conference on Congenital Malformations of the Face and Associated Structures (Pruzansky, 1961)	1960: 1st annual conference on congenital malformations, sponsored by the National Foundation—March of Dimes

* NIDR—National Institute of Dental Research
NIGMS—National Institute of General Medical Sciences

TABLE 3. Formation of Societies in Genetics and Developmental Biology—U.S.A.

Society	*Founded*	*1st Meeting*	*Publication*
American Cleft Palate Association	1943	1943	1951 Cleft Palate Jour.
American Society of Human Genetics	1947	1948	1949 Amer. J. Hum. Genet.
Teratology Society	1960	1961	1968 Teratology
Society for Craniofacial Genetics	1977	1978	1981 Craniofacial Genetics & Developmental Biology
National Society of Genetic Counselors, Inc.	1977	1979	1979 Perspectives in Genetic Counseling

treatment of congenital malformations. Discussion of etiology was a minimal requirement for the article to be included in our survey. The number of publications on syndromes in PRS was almost five times the number in CPJ and JSHD. The number of articles on other subjects studied was similar in CPJ and PRS. JSHD, on the other hand, published comparatively few articles in areas other than syndromes.

Clinical Genetics at CCFA-IL

The seminal influence of Fogh-Andersen's monograph created at least an awareness of the role of genetics among those concerned with clinical management. However, it was not until a cadre of professional staff became available that genetic methodologies began to be applied in the clinical setting. Our first experience in this respect was with the Oral-Facial-Digital syndrome (OFD type I) (Ruess et al., 1962).

In the meantime, the diagnostic profile of our case flow began to change the nature of our center (Figure 1) from a primary cleft lip and palate center to that of a craniofacial anomalies center. This did not mean a reduction in the referral of patients with facial clefts; their actual number continued to rise. What we observed was a proportionately greater number of patients with craniofacial anomalies other than clefts appearing at our clinics.

Coincident with these changes in 1967, we altered our name to represent this larger mission. Integration into the College of Medicine and the University Hospital increased our professional and methodological resources. Inevitably, this led to improved identification of associated anomalies which had been overlooked previously.

Along with others, we found that many patients have multiple congenital anomalies in addition to craniofacial anomalies (Table 5). Sixty-one per cent (864/1396) of the non-cleft patients with multiple anomalies have recognized syndromes. The orientation of the CCFA-IL staff to syndrome identification, the availability of a genetic evaluation, and frequent review of patients' diagnoses partly explains this high percentage. Over 124 syndromes have been diagnosed in our population. Nonetheless, 30% (1242/4180) of the CCFA patient population studied had multiple congenital anomalies for which we could not identify a syndrome or a recognized association of anomalies. Among patients with cleft palate, 54% (436/806) had associated congenital malformations. A similar figure of 55% (189/341) was found in patients with congenital palatopharyngeal incompetence as compared with 35% (472/1365) of patients affected with cleft lip-palate. This observation has been noted by Meskin (1969) reporting on our data and by others (Fraser, 1961; Greene, 1964, 1965; Ingalls, 1964; Knox, 1963).

The occurrence of clefts in syndromes has been well documented (Gorlin, et al., 1976; Cohen, 1978). A comparison of syndromes observed in CCFA patients with those described by Cohen (1978) is presented in Table 6. Since Cohen drew on the literature for his compendium, it is not surprising that his cat-

TABLE 4. Publications on Syndromes, Clinical Genetics, and Developmental Biology in Selected Journals (1960–1978)

Subject	*CPJ (1)*	*PRS (2)*	*JSHD (3)*	*Totals*
Syndromes	21	100	22	143
Population Studies	23	23	4	50
Family Studies	7	5	0	12
Teratogens	14	6	1	21
Chromosomal Disorders	5	1	0	6
Genetic Disorders	8	4	2	14
Embryology Studies	9	14	0	23
Etiology	5	10	0	15
TOTALS	92	163	29	284

(1) CPJ = Cleft Palate Journal
(2) PRS = Plastic & Reconstructive Surgery
(3) JSHD = Journal of Speech & Hearing Disorders

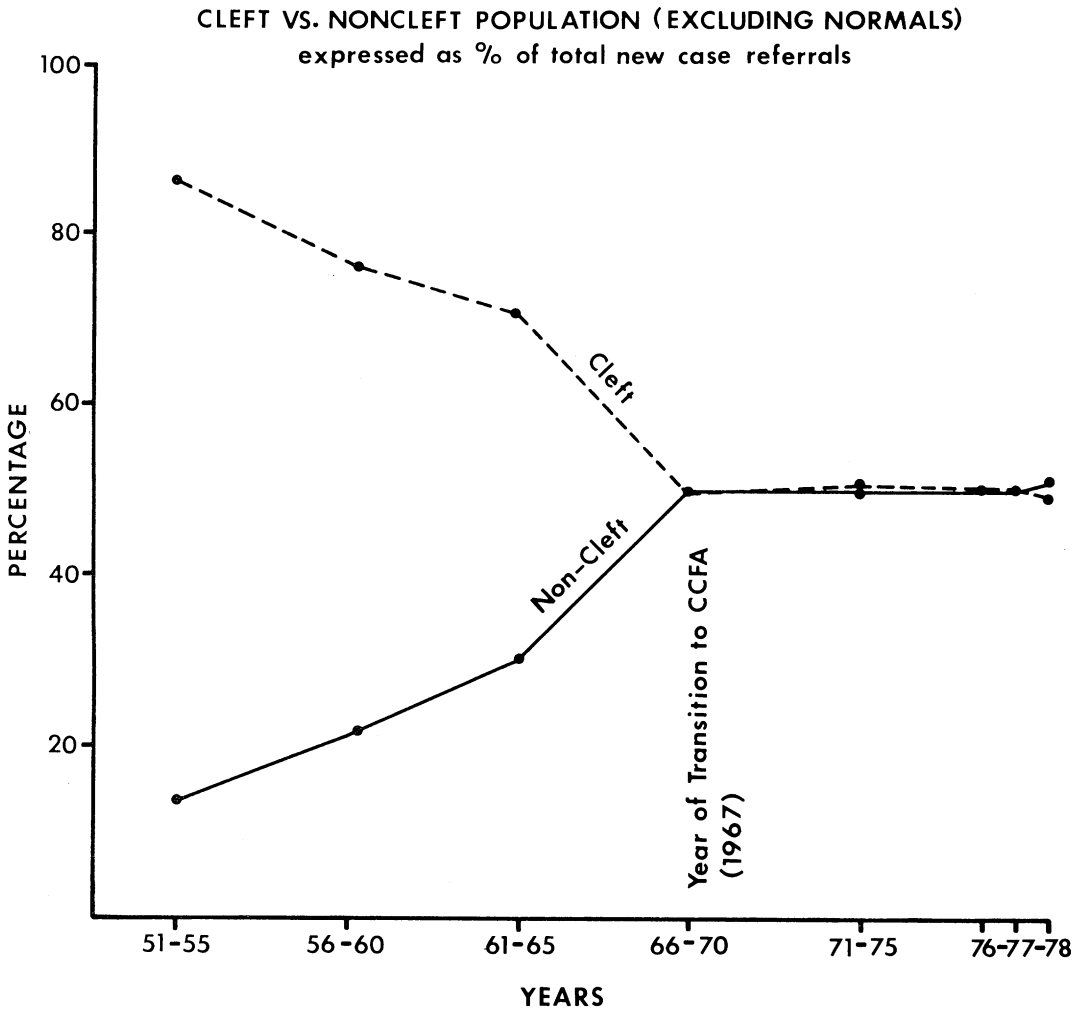

FIGURE 1. Cleft vs. Noncleft Population (Excluding Normals)

TABLE 5. Analysis of Patients with Multiple Congenital Anomalies Observed at CCFA-Illinois

Primary Craniofacial Anomaly	*No Other Anomalies*	*Patients with Multiple Anomalies*			*% with Multiple Anomalies*
		Recognized Syndromes	*Unrecognized Syndromes/Associations*	*Total*	
CL ± P	893	161	311	1365	35
CP	370	167	269	806	54
CPI type I*	152	59	130	341	55
All Clefts†	1415	387	710	2512	44
Craniofacial anomalies without clefts	272	864	532	1668	84
TOTAL	1687	1251	1242	4180	
(% Total)	(40%)	(30%)	(30%)		

* Patients with one or more of the following stigmata: bifid uvula, zona pellucida soft palate, submucous cleft hard palate.

† Excludes median and oblique facial clefts

alog exceeded our own in number of defined entitites. What is of interest is that we identified syndromes not reported by Cohen (Table 7).

We also compared the etiology of syndromes associated with clefting in CCFA patients with those reported by Cohen (1978) (Table 8). Sixteen per cent (175/1097) of patients with clefts and multiple congenital anomalies are affected with syndromes of known monogenic or chromosomal etiology.

Ascertainment Bias

The diagnostic mix of cases flowing into our Center should not be considered representative of their relative frequency in the general population. As a case in point, we draw attention to the composition of patients listed under craniosynostosis (Table 9). This mixture is strikingly different from that reported by Hunter and Rudd (1976, 1977), whose review of the cases on the neurosurgical service at the Toronto Hospital for Sick Children showed a marked predominance of the simple craniosynostoses. Their data were similar to those from other neurosurgical services reviewed in their report. Bertelsen (1958) showed that, on an ophthalmological service, 90% of the patients consisted of the simple craniosynostoses with the remainder presenting syndromes. In contrast, in our sample, 55.8% (91/163) had syndromes.

If we examine the rate at which these referrals accrued during the past 30 years (Figure 2), it is evident that the flow of referrals was relatively low and stable for the first 20 years. With the publication of Tessier's (1971 a, b) surgical results and the subsequent surgery which he performed at our Center from 1972 to 1975, referrals began to escalate. This increase has not plateaued so far.

"Thinking genetics" can have a direct influence on case flow. For example, during the past five years, we gained 65 new patients with the diagnosis of craniosynostosis. Of this number, 11 (17%) were related to a proband in the series. In some instances, the referral source was aware of the familial occurrence and requested genetic consultation for the family. In other instances, our professional staff suspected that other family members were affected and suggested that the relatives be examined. As might be expected, the process identified mild expressions of the disorder. We have experienced a similar increase in case flow of affected relatives of CCFA-IL patients with clefts and other craniofacial anomalies.

Justification for Genetic Diagnosis and Counseling

Genetic diagnosis implies a comprehensive family history and examination of at least first degree relatives by core staff. This includes pedigree analysis. Where indicated, cy-

TABLE 6. Number of Syndromes with Facial Clefts

Category	*CCFA-IL*	*Cohen**	*Known to CCFA but not listed by Cohen*
Syndromes with CL ± CP	17	28	5
Syndromes with CP	30	77	13
Chromosomal Syndromes with Clefts	15	29	3

* Cohen, M. M., Jr. *Cleft Palate J.*, *15*, 306–328, 1978.

TABLE 7. Syndromes with Clefts Observed at CCFA-IL and Not Listed by Cohen*

	Achondroplastic Dwarf
	Holt-Oram
CL + CP	+ Klippel-Feil
	Legg-Perthes
	+ Mandibulofacial dysostosis
	+ Aglossia-adactylia (Hanhart)
	Aicardi
	+ Amniotic band
	BO (R)
	+ Crouzon
Cleft Palate	Ectodermal dysplasia ($\bar{s}$ ectrodactyly)
	Ellis van Creveld
	G - BBB
	+ Hemifacial microsomia, Goldenhar,
	OAV dysplasia
	Hurler
	Idiopathic scoliosis
	Mobius
	Rubella
	47, XXY
Chromosomal	2/9 translocation
	Monosomy 21 mosaic

* Cohen, M. M., Jr., *Cleft Palate J.*, *15*, 306, 1978.
+ Authors are aware of reports by others.

TABLE 8. Etiology of Syndromes with Cleft Lip ± Palate

Etiology	*Analysis of 387 CCFA Cases n (%)*	*Number of Clefting Syndromes CCFA Cases*	*Number of Clefting Syndromes Reported by Cohen**
Total Monogenic	142 (36)	29	79
AD	101 (26)	20	35
AR	25 (6)	5	39
X-linked	16 (4)	4	5
Chromosomal	33 (9)	15	29
Environmental	15 (4)	4	6
Unknown Genesis	197 (51)	11	40

AD = autosomal dominant. AR = autosomal recessive.
* Cohen, M. M., Jr. *Cleft Palate Jour.*, 15, 306, 1978.

TABLE 9. Distribution of Patients with Craniosynostosis

	c̄ Clefts	*s̄ Clefts*
Apert	15 (4CP, 11CPI)	17
Crouzon	5 (1CP, 4CPI)	34
Saethre-Chotzen	5 (2CP, 3CPI)	7
Craniofrontonasal	0	6
Carpenter	0	1
Pfeiffer	0	1
Simple Craniosynostosis	2 (1CP, 1CPI)	70
	27	136

togenetic analysis and other laboratory studies are instituted. We believe that such efforts are warranted on the basis of the following observations in our population:

1. High frequency of multiple congenital anomalies: 60% of all CCFA patients have more than one anomaly (30% in recognized syndromes and 30% in unrecognized syndromes).
2. High frequency of associated anomalies in patients with facial clefts: 35% of patients with cleft lip/palate and 55% of patients with cleft palate have more than one anomaly.
3. High frequency of recognized syndromes in both the cleft sample and the total population combining non-cleft craniofacial malformations.
   a. Sixteen per cent of patients with clefts and other anomalies are affected with syndromes of known monogenic or chromosomal origin.
   b. Fifty-three percent (864/1668) of patients with craniofacial anomalies other than facial clefts have recognized syndromes.
4. Clefting syndromes: 59 syndromes with facial clefts have been identified in our population. Of this number, 15 syndromes have not been previously reported to our knowledge. Forty-four syndromes with clefts are of known monogenic or chromosomal origin.
5. Patients with first or second degree relatives affected with malformations.

CCFA-IL Priorities for Provision of Genetic Counseling are:

1. Patients with disorders known to be monogenic and associated with recurrence risks of 25% to 50%.
2. Patients with known or suspected chromosomal anomalies.
3. Patients of childbearing age.
4. Parents with their first child affected.
5. Patients with other affected family members.
6. Families who request genetic counseling.
7. Patients with disorders of research and service interest, such as hemifacial microsomia and its variants (Kaye et al., 1979).

Actual provision of genetic services is influenced by many factors including patient status and availability of staff. By our criteria, demand and need exceed available resources, and all patients do not receive genetic evaluation and/or counseling.

How are genetic services provided at the CCFA-IL? Approximately 90% of the CCFA patients who receive services from the genetics staff have a confirmed diagnosis and known genetic recurrence risks. Counseling and follow-up for this group of patients are provided by the senior author, who has a master's degree in genetic counseling, with review by

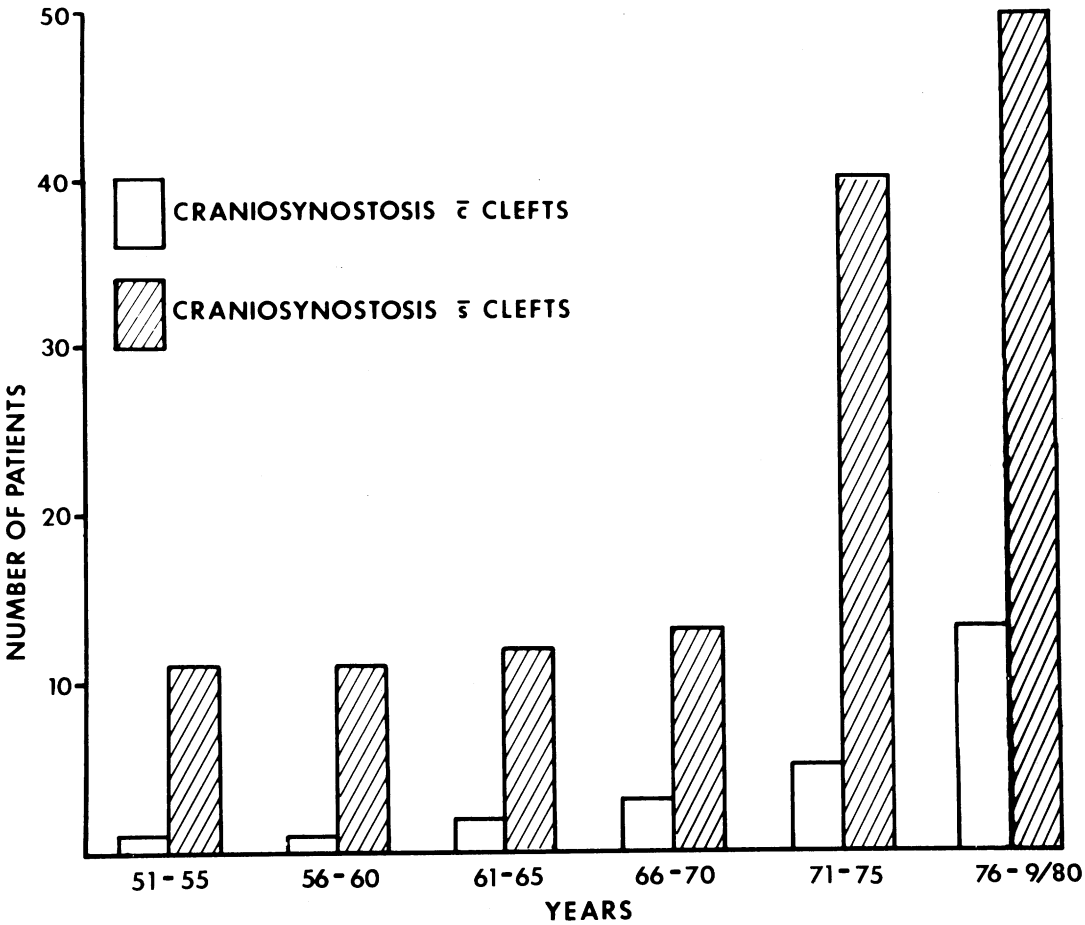

FIGURE 2. Referral Pattern of Patients with Craniosynostosis to CCFA-Illinois, 1951—September, 1980.

a medical geneticist. The full-time participation of a medical geneticist is not required for this group of patients because the Center staff functions as an interdisciplinary diagnostic team with several professionals oriented in medical genetics. The remaining 10% of CCFA patients who receive genetic services have multiple and complex problems. The diagnostic skills of the genetics section are used, along with those of the general staff, to evaluate these patients prior to genetic counseling and follow-up (Figure 3). This model of health-care delivery makes most efficient use of available CCFA genetics staff. As the clinical genetics section at CCFA grows, our goal is to provide genetic evaluation and counseling services to all patients for whom they are indicated.

Summary

Advances in medical genetics and syndrome delineation have demonstrated that many clinical entities are an expression of genetic variability. Assessment of the population at the Center for Craniofacial Anomalies of the University of Illinois Medical Center at Chicago provided a measure of the need for genetic diagnosis and counseling. While it is recognized that this experience is not necessarily representative of that prevailing at other centers, this report provides a basis for interinstitutional comparisons.

Public recognition of the need and consequent demand for genetic services is increasing. The inevitable conclusion is that genetic evaluation and counseling are essential services at a center for craniofacial anomalies.

CASE FLOW INTO GENETICS SECTION CCFA-UNIVERSITY OF ILLINOIS

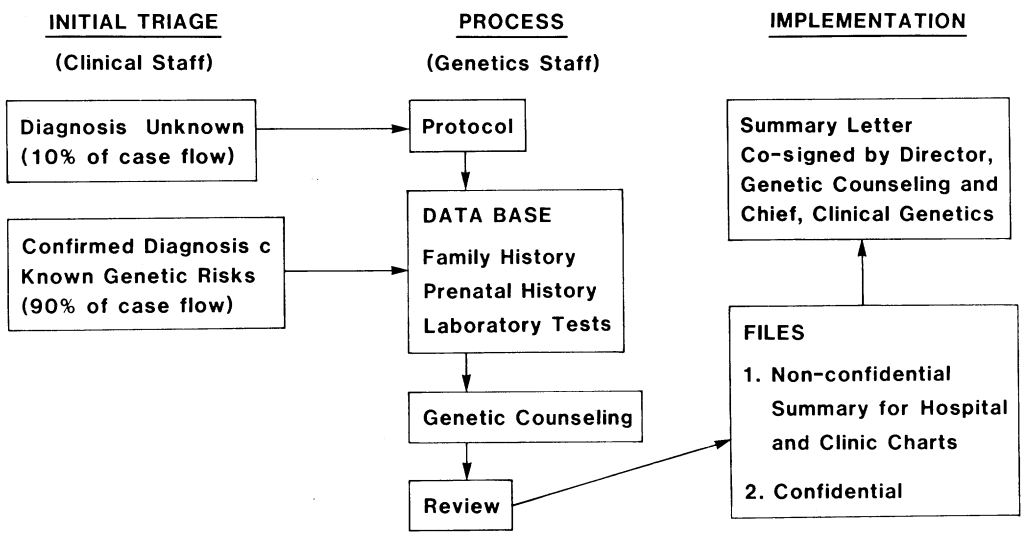

FIGURE 3. Case Flow Into Genetics Section—CCFA Illinois

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