Review:

The Genetics of Cleft Lip and Cleft Palate

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Congenital cleft lip and cleft palate have been the subject of many genetic studies, but until recently there has been no consensus as to their modes of inheritance. In fact, claims have been made for just about every genetic mechanism one can think of. Recently, however, evidence has been accumulating that favors a multifactorial basis for these malformations. In order to review the evidence for and against multifactorial and other concepts of causation, to decide what further data were needed, and to consider possible applications of these concepts to the practical problems of family counseling and prevention, a group of individuals who have been accumulating data on the genetics of these malformations recently met in Bethesda. The workshop was sponsored by the National Institute of Dental Research and attended by Drs. M. S. Adams, H. Bixler, C. S. Chung, F. C. Fraser, R. J. Gorlin, K. Hisaoka, C. C. Knowles, A. D. Merritt, P. Moller, J. D. Niswander, S. Pruzansky, B. L. Shapiro, and C. J. Witkop. Dr. C. M. Woolf was unable to be present but participated by correspondence. Their helpful cooperation in the preparation of this paper is gratefully acknowledged.

I. ETIOLOGICAL HETEROGENEITY

Clefts of the lip and/or palate can be caused by many etiological factors. In a large series of cases it will be found that some are caused by single mutant genes, some by chromosomal aberrations, some by specific environmental agents, and some (the great majority) by the interaction of many genetic and environmental differences, each with a relatively small effect (the multifactorial group).

A. Syndromes

There are now over 50 recognized syndromes, each one rare, that include cleft lip and/or palate as one feature (Gorlin et al., unpublished). Of these, about 60% are manifestations of mutant genes (14 autosomal dominant, 13 autosomal recessive, 3 X-linked), and 40% do not seem to be familial. A specific environmental agent can be implicated in only a very small proportion of cases, although cleft lip or cleft palate does seem to occur occasionally in syndromes caused by teratogens such as rubella and thalidomide. Some of the nonfamilial group of syndromes represent chromosomal aberrations, notably D trisomy, E trisomy, and the XXXXY syndrome.

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Certain mutant genes may cause isolated cleft palate in some cases and cleft lip, with or without cleft palate, in others—for example, the dominantly inherited lip-pit syndrome (Fogh-Andersen 1943; Van der Woude 1954; Cervenka et al. 1967). In other cases, isolated cleft palate appears but not cleft lip, for example, in chondrodystrophia calcificans congenita (25%), the de Lange syndrome (10%), diastrophic dwarfism (25%), and the Smith-Lemli-Opitz syndrome (40%) (Gorlin et al., unpublished). It has been estimated that less than 3% of all cases of cleft lip and/or palate represent a syndrome of some kind and that those with a genetic basis are more likely to have isolated cleft palate than cleft lip with or without cleft palate. Recognition of cases with specific syndromes is important if the families concerned are to be counselled with respect to recurrence risks, and their study may contribute to an understanding of the developmental mechanisms resulting in cleft lip or palate. Furthermore, they should be considered separately in figures stating frequencies of cleft lip or palate in various populations. For instance, the existence of a sex-linked recessive type of submucous cleft palate would give a misleadingly high sex ratio for cleft palate in the British Columbia Indians (Lowry and Renwick 1969) if included with the more usual type in frequency statistics.

After removal of the cases of cleft lip or palate accounted for by mutant genes, chromosomal aberrations, or environmental teratogens, there remains a great majority of cases that can be reasonably attributed to the interaction of several genes and several environmental factors—the multifactorial group.

B. Etiological Distinction between Isolated Cleft Palate and Cleft Lip with or without Cleft Palate

There is strong evidence that in most cases clefts of the secondary palate are both developmentally and genetically different from clefts of the primary palate and lip. Embryological evidence from the mouse shows that cleft of the secondary palate can be induced by teratogens administered after the primary palate has formed, but that failure of the secondary palate to close in embryos with cleft of the primary palate and lip can be a developmental consequence of the abnormalities in the primary palate, not of an intrinsic defect in the secondary palate (Trasler and Fraser 1963). The genetic evidence comes from family studies in which it can be shown that the siblings of patients with cleft lip (with or without cleft palate) have an increased frequency of cleft lip (with or without cleft palate) but not of isolated cleft palate, and that siblings of patients with isolated cleft palate have an increased frequency of isolated cleft palate but not of cleft lip. This was first pointed out by Fogh-Andersen (1942) and confirmed by several others (Fraser and Baxter 1954; Fujino et al. 1963; Woolf et al. 1963). It is a little puzzling that the distinction becomes progressively less clear as the degree of relationship to the proband decreases, and this does not seem to be entirely the result of reporting bias (Moller, unpublished). An exception to the rule is reported from Tasmania (Rank and Thomson 1960), where probands with cleft lip, with or without cleft palate, have an increased frequency of isolated cleft palate (as well as cleft lip with or without cleft palate) among their relatives; Drillien et al. (1966) also reported several discordant parent-child combinations. The Halowar Indians, among whom there is an extraordinarily high frequency of cleft lip,

with or without cleft palate (1/125), and isolated cleft palate (1/234), also show isolated cleft palate and cleft lip with or without cleft palate segregating in the same families. In this case a specific genetic entity, different from the usual type of cleft lip, with or without cleft palate, appears to be segregating; and it is interesting that the family names of this tribe appear also in Tasmania (Witkop, unpublished).

Whatever the explanation for these discrepancies, it is obviously essential, in the collection and analysis of data, to consider isolated cleft palate separately from cleft lip. Throughout this report, therefore, isolated cleft of the secondary palate will be referred to as CP, and isolated cleft of the primary palate and/or lip will be designated as CL, since these are commonly referred to as "cleft lip." Cleft lips that have an associated cleft palate will be designated CLP. Much of the available information combines data on cases of CL and CLP together. These will be referred to as CL(P). Thus we have the following categories: (1) cases of isolated cleft of the secondary palate—CP; (2) cases of cleft of the primary palate and/or lip—CL; (3) cases of CL with an associated CP—CLP; and (4) groups 2 and 3 considered together—CL(P).

II. EPIDEMIOLOGY

A. Reliability of Estimates

Accurate estimates of population frequency are difficult to obtain because of variations in reliability of reporting and the tendency to combine or mislabel cases of CL(P) and CP. Birth certificate information is notoriously unreliable, and, to make matters worse, reliability varies with the type of defect. It has been shown, for instance, that about 90% of children with CLP have this fact recorded on their birth certificates (at least in the central United States), but the figure is only 70% for children with CL and 50% for children with CP (Meskin and Pruzansky 1967). Inclusion of stillbirths may complicate the situation even further. Probably the most reliable figures come from large consecutive series of examined infants, but, in view of the low frequency of the defects, enormously large series must be accumulated to provide adequate amounts of data broken down by social group, race, season of birth, etc.

B. Sex Ratio

More males than females are born with CLP, the proportion ranging from 60% to 80% in various studies (Drillien et al. 1966). The excess of males appears greater in the more severe defects—that is, it is greater for CLP than for CL (Fogh-Andersen 1942; Rank and Thomson 1960) and for bilateral than unilateral (Fogh-Andersen 1942) defects. This is what one would expect on the hypothesis of multifactorial causation, but there are enough exceptions (Drillien et al. 1966; Meskin et al. 1968) that the matter cannot be regarded as settled. It is interesting, though not illuminating, that affected females are more likely to have an additional malformation than affected males (Meskin and Pruzansky, in press).

C. Side of Cleft

In cases of unilateral CL or CLP, about two-thirds are on the left side, both for CL and CLP. There is an associated cleft palate more often with bilateral (86%) than with unilateral (68%) clefts of the lip. This is consistent with the idea that the cleft

palate associated with cleft lip is secondary to the lip defect, and hence more likely to occur when the lip defect is more severe. This idea was pointed out by Fogh-Andersen (1942) and received experimental support from studies in the mouse (Trasler and Fraser 1963).

D. Environmental Factors

No striking associations occur between CL(P) or CP and environmental variables such as social class, season of conception, and parental age, though there may be a small increase in incidence of CL(P) with increasing parental age (Fraser and Calnan 1961; Woolf 1963; Greene et al. 1964; Meskin and Pruzansky 1968).

E. Variation between Populations

Estimates of frequency of CL(P) range from 0.6 to 1.8 per thousand births in various reasonably reliable studies, with CLP being 1.5–3 times as frequent as CL (Drillien et al. 1966). In a recent large study on hospital births, considering only samples of over 10,000 births, the range was from 0.60 in Czechoslovakia to 1.52 in Santiago (Stevenson 1966). The frequency of CP has been estimated as between 0.39 and 0.50 per 1,000 births in various studies (Drillien et al. 1966).

It is difficult to know how much of the variation represents differences in racial frequencies, geographic variations in teratogenic factors, or differences in reporting. In relatively small series, variation could even represent the presence or absence of large families with one of the rare, strongly genetic forms of CL(P). Fogh-Andersen's claim (1961) that the frequency is slowly increasing in Denmark needs to be tested in other populations.

F. Racial Variation

The greatest contribution to variation in population frequency is probably that associated with race. Knowledge of incidence and its variation among racial groups could provide useful genetic information in addition to its significance from the standpoint of public health. The reported incidence estimates of CL(P) in Caucasian populations vary from 0.6 to 1.7 per 1,000 population. Among the highest estimates of incidence in Caucasians is 1.78 per 1,000 population obtained from a recent exhaustive population survey made in Iceland (Moller, unpublished). The mean incidence in Caucasians is approximately one per 1,000 population.

There is a higher incidence of CL(P) among Japanese in Japan (Kobayashi 1958; Neel 1958). The mean incidence is about 1.7 per 1,000 births. The excess appears to consist largely of females with CL, a curious phenomenon for which no explanation is apparent. Perhaps an ascertainment or coding bias is involved. There is no suggestion of a genetically different type of cleft lip, without cleft palate, peculiar to the Japanese in the data of Fujino et al. (1963). That is, female CL probands do not have a higher frequency of siblings with CL (1.1%) than do male probands (1.4%), as one might expect if there were a genetically distinct type of CL occurring preferentially in females. There is no suggestion of a sex-ratio difference between CL and CLP among the Japanese in Hawaii, though in general the sex ratio is reduced in CL(P)—1.3 male

to one female (Chung, unpublished). However, Hawaiians exhibit a lower population incidence than Orientals.

In Hawaii, offspring of crosses between races differing in frequency of CL(P) have an intermediate frequency—suggesting that the underlying genetic factors act additively (Morton et al. 1967). Interracial crosses provide no evidence of a maternal effect on CL(P) frequency (Morton et al. 1967).

Negroes appear to have lower risks than Caucasians for many congenital malformations including CL(P) (Greene et al. 1964; Altemus and Ferguson 1965). Recent data collected on a strictly standardized protocol by the National Institute of Neurological Diseases and Stroke (NINDS) collaborative perinatal study substantiate these findings, giving a frequency of 0.41 per 1,000 births (Chung and Myrianthopoulos 1968).

Thus it is well established that racial heterogeneity exists in the incidence of CL(P), with the Mongoloid races having higher frequencies than Caucasians, and Caucasians higher than Negroes. There appears, therefore, to be no need for further collection of data for the sole purpose of estimating incidence. However, racial comparisons may be useful in testing etiological hypotheses, and it will be of some value to have more information on the incidence of CL(P) in non-Japanese Orientals and Negroes in their respective lands of origin. Furthermore, as will be seen, simultaneous studies of incidence, sex-ratio distribution, and genetic risk of relatives of different degrees for various population groups are expected to yield information useful for testing certain genetic hypotheses.

Racial variation in the incidence of isolated cleft palate is less obvious than in that of CL(P). There is considerable overlapping of the incidence estimates between races. Though some estimates for Japanese in Japan—0.55 per 1,000 (Neel 1968)—and American Indians—0.59 per 1,000 live births (Niswander and Adams 1967)—tend to be higher than those of Caucasians, no significant differences are detected in comparisons of various racial groups including these two races in Hawaii (Morton et al. 1967). No differences were detected between Caucasians and American Negroes (Altemus and Ferguson 1965; Chung and Myrianthopoulos 1968). Thus any racial differences there may be in the frequency of CP appear negligible compared with those for CL(P).

III. THE MULTIFACTORIAL CONCEPT—QUASI-CONTINUOUS VARIANTS

Many common congenital malformations result from a developmental process failing to reach some kind of developmental end point, or threshold. The rate of the developmental process is influenced by many factors, both genetic and environmental, and can be considered a continuously distributed variable. Failure to reach the threshold results in abnormality—thus the continuously distributed variable is separated into discontinuous classes, normal and abnormal. Such traits have been called "quasi-continuous" variations (Gruenberg 1952). In the case of cleft palate in mice, for instance, the continuous variable can be considered that developmental stage at which the palate shelves move from their position lateral to the tongue to the "horizontal" plane above the tongue. Many factors, genetic and environmental, interact to determine when this occurs in the embryo. If it has not occurred by a certain stage of growth, the shelves will be unable to reach each other to fuse, and a cleft palate re-

sults (Fraser et al. 1957). This stage can be considered a developmental threshold, distinguishing between normal embryos and those that will have cleft palate.

According to this model, the familial distribution of a trait that results from quasi-continuous variation should have certain characteristic features (Carter 1964, 1965, 1969), and evidence has been accumulating for some time that CL(P) fits the model (Fraser 1963; Carter 1965). The threshold will be near one tail of the distribution, say the right-hand one. An affected individual lies beyond the threshold, by definition. A number of deductions can then be made about the frequency of the trait in the near relatives.

A. Relationship between Population Frequency and Frequency in Relatives

Using the threshold model, and making a number of reasonable assumptions, it is possible to derive a relationship between the frequency of the condition in relatives and the frequency in the general population. For instance, if the phenotypic correlation between first-degree relatives is 0.5 (that is, heritability is high), the frequency in first-degree relatives in proportion to the population frequency approximates the square root of the population frequency (Edwards 1960). For simple modes of inheritance the relationship is quite different. A number of conditions have been shown to fit this criterion for multifactorial causation, including congenital hypertrophic pyloric stenosis, situs inversus (Newcombe 1963) and atrial septal defect (Nora et al. 1967). For CLP, using a population frequency of one per 1,000, this relationship would lead one to expect a recurrence risk in siblings of 3.2%, which is well within the observed range (Fogh-Andersen 1942; Curtis et al. 1961; Woolf et al. 1963). In the case of CP, assuming a population frequency of one in 2,500, the expected recurrence risk would be 2%, also a close fit to the observed values.

B. Rapid Decrease in Frequency with Decreasing Degree of Relationship

For a trait determined by a single gene, thefrequency in near relatives will decrease by 50% with each degree of relationship removed from the proband.

For a quantitative character, the distribution of the trait in the population approaches a normal distribution. If many genes contribute to the genetic component, each with a small effect, there will be a phenotypic correlation between first-degree relatives approaching 0.5 if the environmental contribution to the variation is small. Thus, if one chooses probands near the tail of the distribution and measures the trait in the first-degree relatives (who have about half their genes in common with the proband), the distribution of the trait will have a mean halfway between the mean of the probands and the mean of the population. For second-degree relatives (who have one-quarter of their genes in common with the proband) the mean of the distribution will be one-quarter of the distance from the population mean to that of the probands. For third-degree relatives it will be one-eighth of the distance, and so on. Now, if one imposes a threshold on the model, such that only individuals who lie a given distance from the mean will be affected, the proportion of affected relatives will depend on the number of individuals who fall beyond the threshold in the respective distribution. Thus, if the distance from the mean of the probands to the population mean is 1, the distance for first-, second-, and third-degree relatives will be one-

half, one-quarter, and one-eighth, respectively. However, the proportions of affected relatives will be represented not by these ratios but by the area under the curve beyond the threshold in the respective distribution. Since the tail of the curve becomes progressively flatter, the drop in frequency between first- and second-degree relatives should be greater than that between second- and third-degree relatives. This has now been shown to be so for several common congenital malformations, including congenital hypertrophic pyloric stenosis, congenital dislocation of the hip, talipes equinovarus, and CL(P) (Carter 1965, 1969).

This model assumes a "vertical" threshold—that is, all those who lie beyond the threshold are affected. This may be appropriate if one is considering only genotype and the genetic predisposition, rather than whether the individual is clinically affected. In real life it is more appropriate to consider also the environmental contribution to predisposition. Falconer (1965) does this by using the term "liability" to refer to the position of an individual with respect to the distribution as determined by both genetic and environmental factors, and Edwards (1969) retains the genotypic distribution but assumes that the probability of being affected increases with increasing genetic susceptibility. That is, the threshold is not vertical but sloping. If the increase is assumed to be exponential (which is probably incorrect, but a reasonable approximation), the model becomes more amenable to mathematical analysis (Edwards 1969). So far, no one has critically tested the fit of the observed figures to these models. Carter (1969) has shown that the data fit the multifactorial expectation quite well, assuming that three per 1,000 of the population lie beyond the threshold and one of these is clinically affected. Heritability, estimated on the basis of the Falconer model, would be about 80% for CL(P) (Falconer 1965)—a value higher than one would expect, from the low recurrence risk, on a simpler genetic model.

C. Risk for Relatives versus Population Incidence

A corollary of the previous principle is that in groups where the frequency of the condition is increased, the risk for relatives should also be increased, though not proportionately. This appears true for pyloric stenosis and congenital dislocation of the hip, where the two groups compared are males and females, one sex having a higher frequency than the other (Carter 1969). It would also presumably hold true for a condition measured in two different populations, but only if the difference results from a shift in the mean relative to the threshold, rather than a change in variance of the distribution. On this basis the recurrence risk for siblings should be higher in Japanese than in Caucasians, but the limited data available do not bear out this expectation (Fujino et al. 1963). Further studies are needed.

D. Twins

For any condition determined in part by genetic factors, the concordance rate is expected to be higher in monozygotic (MZ) than in dizygotic (DZ) pairs. Data on twins with cleft lip or cleft palate, ascertained without respect to concordance, are fairly scanty but do show a higher concordance rate in monozygotic pairs (table 1).

These figures confirm that the familial tendency is likely to be the result of genetic, rather than environmental, familial factors; but, because of certain statistical com-

plications, including those resulting from a common uterine environment, they are not very useful for estimating heritability (Falconer 1965). If the value for CP, for dizygotic pairs, is really as high as 10% (i.e., significantly higher than the rate for sibs), the existence of maternal factors is implicated. Twin data are notoriously subject to bias (Metrakos et al. 1958), and more information is needed, particularly for DZ pairs.

With respect to a study of 19 sets of twins, many of whom had been under observation since infancy and prior to surgical intervention, it was noted that previous estimates of concordance of clefts among monozygotic twins may have been understated (Pruzansky et al. 1969). For one thing, there has been confusion of terminology regarding expressivity. When monozygotic twins did not present similar clefts, they were sometimes labeled as discordant, even though they were both affected. The

TABLE 1

CONCORDANCE RATES (%) IN CO-TWINS OF PROBANDS WITH CL(P) OR CP (SUMMARIZED BY GORLIN)

	CL(P)		CP	
	N	Concordance (%)	*N*	Concordance (%)
MZ.....	53	37.7	17	23.5
DZ.....	86	8.1	20	10.0

NOTE.—CP = isolated cleft of the secondary palate, CL = isolated cleft of the primary palate and/or lip, CLP = CL with an associated CP, and CL(P) = CL and CLP considered together.

major cause of underreporting is probably the failure to note minor defects of the palate such as those described for congenital pharyngeal incompetence.

The main value of twin studies may be for the identification, in discordant monozygotic twins, of the facial features associated with a disposition to facial clefts, but so far little has been attempted along these lines.

E. Risk of Recurrence after Two Affected

According to the threshold model, unaffected parents who have had an affected child have declared themselves to carry more than the average number of genes contributing to the condition. That is, on the average, they will be situated between the mean and the threshold value. Thus the risk of their subsequent children being affected is above average (i.e., the condition is familial). If a second affected child is born, the parents can be assumed to carry still more predisposing genes and to be still closer to the threshold. Thus, the risk of recurrence in subsequent siblings is higher when the parents have already had two affected children than after one affected. This is contrary to expectation for simple modes of inheritance and is one of the distinguishing characteristics of multifactorial inheritance.

In the case of CL(P), the risk for siblings born of unaffected parents increases from about 4% after one affected child to 9% after two affected (Curtis et al. 1961). No

increase was detected for CP, but the numbers were small and more data are needed. A similar effect has been shown for anencephaly and spina bifida (Carter and Roberts 1967).

F. Effect of Affected Near Relative on Recurrence Risk

If the existence of an affected first-degree relative increases the recurrence risk, it is reasonable to suppose that the same will be true for affected relatives of more distant degree, though the increase would be smaller.

In the case of CL(P) no such increase has yet been demonstrated (Curtis et al. 1961), but the published material combines data for second- and third-degree affected relatives, and it would be useful to obtain data for families with affected second-degree relatives separately.

For CP, the recurrence risk was markedly increased in cases with a positive family history in a Danish series (Fogh-Andersen 1942), less so in a Montreal series, and not at all in a Toronto series (Curtis et al. 1961). If the increase is real, it is difficult to reconcile with the lack of increase in risk after two affected siblings (if that is real!). Perhaps the differences between series may result from inclusion of several families with a strongly inherited type of CP in some series and not in others. Further data may clarify the situation.

G. Recurrence Risk Varies with Sex of Proband

In traits that occur more frequently in one sex than the other it must be assumed that the threshold is nearer the tail of its distribution in the sex less often affected. For CP this could mean that palate closure occurs later in development in females than in males, and it is gratifying that such appears to be the case (Burdi 1969). If patients of the sex less often affected are nearer the tail of the distribution, they should have more predisposing genes than patients of the other sex. Therefore, the frequency of the trait in the near relatives of a patient ought to be higher when the patient is of the sex less often affected. This was first demonstrated for congenital hypertrophic pyloric stenosis (Carter 1965), where there is a pronounced excess of affected males, and the frequency of affected first-degree relatives is much higher when the proband is a female than when it is a male.

This relationship appears to be true also for CL(P) (Woolf et al. 1964; Tanaka et al. 1967; Fujino et al. 1967; Carter 1969) and for CP (table 2).

Thus for CL(P), where males are more likely to be affected, the recurrence risk is higher for the siblings of females, and the reverse is true for CP.

H. Recurrence Risk Varies with Severity of Defect in the Proband

According to the threshold model, a severely affected case would lie nearer the tail of the distribution, and would be expected to be more genetically predisposed than a mild case. Thus the frequency of affected relatives should be higher in the more severely affected cases.

This has been shown to occur for CL(P) in the combined series from Copenhagen and London (Carter 1965); the recurrence risk for siblings of probands was 5.7% in the case of bilateral CLP, 4.2% for unilateral CLP, and 2.5% for unilateral CL. The

Montreal data do not conform (5.6%, 3.9%, 3.8%) but the numbers are small (195, 414, 120). The combined data for Copenhagen, London, and Montreal are given in table 3. (Cases of bilateral CL are so rare that they are excluded, but it would be interesting to obtain such figures.)

I. Microforms

There is some confusion about the question of microforms of CL(P). Strictly speaking, one might accept as microforms only what would be considered as minor

TABLE 2

EFFECT OF SEX OF PROBAND ON RECURRENCE RISK IN SIBS FOR CL(P) AND CP, RESPECTIVELY

SEX OF PROBAND	CL(P)		CP	
	No. Sibs	% Affected	No. Sibs	% Affected
♂	1,908	3.9	96	6.3
♀	1,008	5.0	239	2.3

SOURCE.—CL(P): combined data of Carter (1965), Woolf et al. (1964), and F. C. Fraser (unpublished); CP: F. C. Fraser, unpublished data.

TABLE 3

RECURRENCE RISK FOR SIBLINGS ACCORDING TO SEVERITY OF DEFECT

Proband Has	No. Sibs	No. Affected	% Affected
RL CLP	658	37	5.62
R or L CLP	1,696	70	4.13
R or L CL	797	21	2.63

degrees of cleft lip, such as a scar in the appropriate place or a notch in the alveolus. Somewhat more loosely, but perhaps more logically, one might accept any developmental deviation that indicated the person concerned had been near the developmental threshold for a cleft lip. Whichever criterion is chosen, the feature in question should be demonstrably more frequent in the near relatives of affected individuals than in the general population, and it may be difficult to get adequate data on a suitable control population. Lack of such controls has detracted from a number of claims for microforms of CLP. Woolf et al. (1965), in a well-controlled study, have shown that missing or anomalous lateral maxillary incisors is not a microform of CL(P). A tendency to hypertelorism has been reported in CL(P) patients—especially familial ones (Niswander, unpublished)—but another survey reports hypotelorism (Bixler, unpublished). Studies by Mills et al. (1968) and by Pashayan and Fraser (unpublished) have not borne out the suggestion (Fukuhara 1965) that nostril asymmetry is a microform of CL(P). Other investigators (Fukuhara 1965; Rusconi and

Brusati 1966) have claimed that bony defects in the nasopalatal segments, detected by laminography, are microforms, but this finding could not be verified by Niswander (1968) using a larger sample and a control group. Data on these and other possible microforms are being accumulated in several centers.

Bifid uvula occurs with increased frequency in near relatives of patients with CP and is presumably a microform of cleft palate (Meskin 1963). It has an unusually high frequency in the Chippewa and Navajo Indians, who also have a high frequency of CL(P). Palate asymmetry is reported in the near relatives of patients with CP, though there is no difference in the average measurements (Shapiro, unpublished; Pashayan and Fraser, unpublished).

Congenital palatopharyngeal incompetence (CPI), a condition in which the individual speaks as if he has a cleft palate but does not have an overt cleft, may be considered as a microform of CP, though its clinical importance makes the term seem unsuitable. It can also be regarded as an example of a multifactorial system with a threshold at the point where the velum is unable to valve the nasopharyngeal port. The defect may result from a deficiency within the velum itself or from a variety of anatomical factors that contribute to an increased diameter of the nasopharynx, such as anomalies at the base of the skull and upper cervical column (Pruzansky, unpublished).

In a series of 110 cases of CPI studied at the Center for Craniofacial Anomalies of the University of Illinois Medical Center, 81% presented one or more of (*a*) bifid or absent uvula, (*b*) zona pellucida of the soft palate and/or short soft palate, and (*c*) submucous cleft of the hard palate. Those cases which did not reveal such stigma (19%) demonstrated other findings on radiographic examination which could account for the physiologic defect. These included a thin soft palate, or increased depth of the nasopharynx due to occipitalization of the atlas, or atlantoaxial dislocation wherein the anterior arch of C_1 was tilted upward and situated immediately superior to the odontoid process. Since the presence of a large adenoid facilitates velopharyngeal valving, it is not surprising that 25% of the CPI cases were unmasked by adenoidectomy. Removal of the adenoids resulted in persistent hypernasality not remedied by speech therapy (Pruzansky and Mason 1966).

It appears, then, that a multifactorial causality is involved that includes one or more of the following structures: uvula, soft palate, hard palate, upper cervical vertebrae, skull base, and adenoid. Conceivably, a patient may possess all of these stigmata but can be "protected" by a large adenoid mass. The presence of a bifid uvula, per se, does not necessarily indicate CPI. It should, however, be considered as a contraindication to adenoidectomy pending radiographic evaluation of the velopharyngeal structures.

The greater frequency of overt clefts of the lip and/or palate among relatives of such individuals, as well as the presence of CPI in one monozygotic twin where the other possessed a cleft palate, suggested that CPI was part of a continuum with cleft palate. If this is so, then the prevalence of clefts and microforms is far greater than has been estimated previously.

A microform that occurred frequently in the near relatives, and infrequently in the general population, would be useful for counseling. For example, in the Robin syn-

drome (usually sporadic) it is probable that the cleft palate results from failure of the mandible to grow downward and forward from the skull base at a critical stage of development, thus leaving the tongue between the shelves and impeding shelf movement. In some cases the shelves may succeed in closing in spite of the delay, and the baby would have micrognathia without cleft palate. The micrognathia diminishes with age, so an affected adult may have a facial profile within the normal range. However, a recent study has shown that the mandible in patients with the Robin syndrome retains a peculiar shape and proportion, demonstrable by X-ray in the adult (Pruzansky and Pavlick, unpublished), and it will be interesting to see if this trait has a familial distribution.

J. Parental Consanguinity

The association of rare, recessively inherited diseases with parental consanguinity is well known. Less widely recognized is the fact that the frequency of multifactorially determined conditions can also be expected to be elevated in the offspring of consanguineous matings. This results from the fact that consanguinity increases homozygosity, which will increase the proportion of individuals at the tails of the distribution (Newcombe 1963).

Data on the frequency of CL(P) and CP in the offspring of consanguineous matings are scanty because of the difficulty of ascertaining cousin marriages in an unbiased manner. The largest body of suitable data on offspring of cousin marriages does not reveal an increased frequency of CL(P) or CP (Schull and Neel 1965), nor do several other studies (Sutter and Tabah 1954; Slatis et al. 1958).

Another approach to the problem is to look for an increase in parental consanguinity in the parents of affected children. Here also there is no convincing evidence of a consanguinity effect (Fogh-Andersen 1942; Fujino et al. 1963).

A third way to look for an effect of consanguinity is to compare the recurrence risk in siblings of probands whose parents were consanguineous or unrelated. Again no effect of consanguinity has been observed (Curtis et al. 1961).

For CP an increase in the frequency of consanguineous parents has been found in Japan (Fujino et al. 1963). Further data are needed.

K. Maternal Effects

As mentioned previously, data from interracial crosses provide no evidence that maternal factors influence predisposition to cleft lip. There is a slight tendency for the incidence to be higher in maternal than paternal relatives in the data of the Montreal and Toronto series, but this could be due to reporting bias.

Little data are available as to prenatal factors that might be associated with cleft lip. Prospective data must be collected in vast amounts to obtain enough information on any one kind of defect, and so far no prenatal factors have been identified by such studies. Retrospective studies, on the other hand, are subject to memory bias in reporting. It has been shown, for instance, that emotional stress is reported in pregnancies resulting in children with CL(P) more often than in the other pregnancies of the same mother, but that the same difference is found between pregnancies of control subjects and their siblings—the controls having some genetically determined disease

clearly not due to prenatal stress (Fraser and Warburton 1964). This means also that normal subjects are unsuitable as controls for such studies.

Drillien et al. (1966), in Edinburgh, found an increase of threatened abortion and of severe vomiting in pregnancies leading to CL(P) or CP. Data from Montreal (F. C. Fraser, unpublished) support the findings with respect to maternal bleeding (17.0% for CL(P) mothers, 9.2% for controls) but not vomiting (13.9% vs. 11.3%). Conversely, the Montreal study suggests an increase in toxemia in the CLP and CP series, but this is not supported by the Edinburgh series. Maternal reproductive-tract pathology was reported by 11.2% of 269 mothers of CL(P) children and 5.7% of 142 control mothers. No convincing differences were shown for maternal first-trimester weight loss (7.9% vs. 10.2%), attempted abortion (5.2% vs. 3.1%), first-trimester febrile diseases (3.9% vs. 4.2%), first-trimester medication (17.9% vs. 19.6%), menstrual irregularities, weight at conception, and numerous other comparisons. Suggestive findings might be further studied in prospective series such as that of the Collaborative Study on Perinatal Mortality of the National Institutes of Health.

L. Developmental Instability

Theoretically, cleft lip or cleft palate could occur as the result of a generalized developmental instability rather than a developmental deviation restricted to the face. This would account for the increase in other major malformations noted in children with CL(P) and CP. If the general instability resulted from a specific teratogen with a familial tendency, it might affect the face in embryos already predisposed by the genotype but also other organs that might be susceptible. In either case, this would lead to an increased frequency of other malformations in the near relatives of probands with CL(P) or CP. Several studies have reported no such increase (Rank and Thomson 1960; Curtis et al. 1961), but others have (Fogh-Andersen 1942; Drillien et al. 1966; Niswander and Adams 1968). Some of the variation in results may stem from differences in the number of syndromes recognized and excluded from the data in various studies. Drillien et al. (1966) found that the increase occurred mainly in families where the family history was negative for clefts of lip and palate, which one might expect if a proportion of cases resulted from generalized developmental instability. Further study of differences between familial and nonfamilial cases is needed.

Significant in this regard is the observation (Adams and Niswander 1967) that children with familial CL(P) have an increased asymmetry, both for the atd angle in the palmar dermatoglyphics, and for size of the first molar tooth. This would suggest that the affected child is developmentally unstable for other features than the lip and palate. This asymmetry was not increased in the parents or sibs of affected children, suggesting that the postulated instability was not familial.

M. Nature of the Underlying Distributions and Thresholds

From the preceding discussion it appears that there is an impressive amount of evidence supporting the idea that in the majority of cases CL(P) is a threshold character with a multifactorial etiology. For CP the data are less voluminous and less convincing, and there is need for considerably more information. A cooperative pooling of

data collected by participants in the conference is planned, to provide larger numbers in the hope of clarifying some of the moot points discussed.

If the etiology is indeed multifactorial, involving a developmental threshold, what are the implications? First, the effects of the underlying genes will be harder to distinguish than they are in conditions showing simple modes of inheritance. There will probably be no identifiable biochemical defect. Second, the condition is likely to have a more stable frequency than those due to single-gene differences, and will be relatively little affected by changes in mutation rate, relaxed selection resulting from improved treatment, or eugenic selection.

Further progress should be directed toward identifying as many as possible of the factors concerned, and particularly toward an understanding of the underlying developmental variables and thresholds. Experimental studies in mice have suggested that in the case of CP, the important variable is the stage at which the palate shelves become horizontal above the tongue, and the threshold is the latest stage at which the shelves can reach each other to fuse when they do come up. There are many ways in which the relation of distribution to threshold can be altered to increase the probability that the embryo will fall beyond the threshold—increased head width, increased tongue size, reduced tongue mobility, reduced mandible growth, reduced shelf width, reduction in the force that causes the shelf to move, etc. Which of these could be identified, in lesser degree, in the parents, and thus serve as an indicator of genetic predisposition? Which could be modified by environmental means to reduce the probability of cleft palate? Further experimental studies may be useful here. If, for instance, we could learn how to make the palate shelves close earlier in development, we could apply this in high-risk cases (e.g., sibs or offspring of affected individuals) and thus markedly reduce the recurrence risk.

For CL(P) there is less evidence of the nature of the distribution and threshold. Experimental studies suggest that face shape may be relevant (Trasler 1968), and there is some evidence that this is true also for man. Parents of children with CLP tend to have larger bizygomatic distances, flatter maxillae, thinner upper lips, and longer nasion-chin measurements than controls (Pashayan and Fraser 1969). Further studies, with carefully matched controls, are needed along these lines. Carter and Wilkinson (1964) have shown for congenital dislocation of the hip how specific important factors can be identified among the many variables involved in a multifactorial system. Perhaps this can also be done for cleft lip and cleft palate. It is by such a rational approach that the way to prevention may be found.

IV. CONCLUSIONS

An impressive amount of evidence is accumulating in support of the concept that CL(P), in the majority of cases, represents a quasi-continuous variant, or threshold character of multifactorial etiology. Some contrary evidence from interracial comparisons (no increase in recurrence risk in races with an increased frequency) needs further testing. The published data are still inadequate for testing the hypothesis with respect to CP.

There is no need for further studies on incidence except to test specific hypotheses, such as the correlation of incidence with face shape or other anthropometric features.

Quantitative embryological studies of lip formation and palate closure are desirable to gain understanding of the developmental variables and thresholds involved. For instance, one could predict that cleft palate is more frequent in females than males because females close their palates later in development, and this appears to be so (Burdi 1969), thus supporting the threshold concept for CP. Are there embryological differences to account for other differences, for instance that CL(P) is more frequent in males, and occurs more often on the left side?

Further progress may be made by additional studies designed to test specific hypotheses and making use of particularly advantageous material such as syndromes involving CL(P) or CP, high-risk families, and monozygous co-twins of patients. Observations on arch form, face shape, and body asymmetries could be useful in helping to identify specific factors among those underlying the predisposition to clefts.

In many cases the appropriate material may be so rare that no single investigator will be able to make an adequate number of observations. An increase in the number of collaborative studies would therefore be desirable. One practical result of the workshop was the planning of a collaborative project to pool the data of the participants in order to find answers to some of the open questions raised in this report.

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