Problems and Methods in Research on the Genetics of Dental Occlusion

RICHARD J. SMITH, D.M.D., M.S.*

HOWARD L. BAILIT, D.M.D., Ph.D.**

Research on the genetics of dental occlusion has had little impact on the daily practice of clinical orthodontics. Although it is recognized that genes contribute to variation in occlusion, treatment objectives and therapeutic methods do not reflect the genetic differences among individual patients. This is in spite of over 100 years of interest in the relationship between genes and occlusal variation that has continued unabated to the present time.

There are two major reasons for this lack of progress. First are the inherent limitations of genetic research on human populations. The second and more important factor has been the concept of malocclusion and some of the basic assumptions and methods used in its study by orthodontic researchers.

The purpose of this paper is to critically review the status of research on the genetics of dental occlusion, to make suggestions for the direction of future research that incorporate objectives of clinical significance, and to discuss some of the methodological problems that will be encountered in such efforts.

REVIEW OF THE LITERATURE

This review will not attempt to provide a comprehensive historical perspective or to consider all recent studies related to the genetics of occlusion. As a critical evaluation, only selected publications will be discussed. Readers interested in more bibliographic reports are referred to Weinberger,[78] Brash, McKeag and Scott,[9] Krogman,[41,42] Jago[40] and Isaacson et al.[39]

Most genetic studies of dental occlusion have been concerned with one or more of five specific objectives: (1) modes of inheritance, (2) admixture and inbreeding effects, (3) linkage analysis, (4) heritability, and (5) population differences. Prior to a discussion of each of these, it is important to note that they can be further organized into two groups: the first four, which require family pedigree data for study, and the fifth, which is based on random samples of total populations. Most orthodontic research has been concerned with family analysis and has given less consideration to the population genetics of occlusal variation. However, as will be pointed out, investigations utilizing both types of data are necessary for a thorough understanding of the genetic contribution to variation in occlusion. Each of these five issues will be discussed.

Mode of inheritance

Most recent studies have concluded that occlusal variation is polygenic, i.e., controlled by both many genes and various environmental influences.[32,33,47,60] This statement refers to the normal range of variation, because it is well-recognized that extreme deviations are generally due to chromosomal or single gene defects.[68] Some workers have noted that strong familial similarities within normal boundaries could also be due to single major genes.[23,63] This may be an explanation for the famous "Hapsburg jaw" and has been sug-

*Assistant Clinical Professor, Department of Orthodontics, University of Connecticut School of Dental Medicine and University Fellow, Department of Anthropology, Yale University.

**Professor and Head, Department of Behavioral Sciences and Community Health, University of Connecticut School of Dental Medicine.

gested as the basis for Class III malocclusion in some eastern Aleut families.[52]

The observations on human subjects have been supported by the results of animal experimentation. Studies on cattle by agricultural workers also suggest a general polygenic mode for occlusal variation[79] but demonstrate the potential for extreme effects from single pathological genes.[27] The possibility of single gene effects within the normal range of variation was demonstrated in a significant investigation by Gruneberg and Lea.[29] They found an autosomal recessive gene to cause a relatively shortened mandible and resultant retrognathia in long-haired dachshunds which otherwise remained fully viable and healthy.

Since alternative mechanisms may operate in different families, it is probably incorrect to assign a specific mode of inheritance to any type of occlusal variation. While polygenic inheritance has been emphasized in the orthodontic literature in recent years, single genes cannot be ruled out in the etiology of some of the strong similarities between sibs or parents and children that are often encountered in clinical practice.

Admixture and inbreeding effects

Many investigators have contended that racial admixture increases the occurrence of malocclusion.[6,26,37,43,49] In fact, the only detailed study of this possibility, conducted by Chung et al.[13] on several thousand racially mixed children in Hawaii, concluded that human racial crossings presented no risks to dental occlusion.

Much of the opinion regarding an adverse effect of racial admixture originates in the work of Stockard and Johnston.[73] After examining hybrids of numerous matings between pedigreed dogs, they concluded that the length of the upper and lower jaws were inherited independently, and that this was responsible for the "widespread disharmony in facial types commonly seen in race and breed hybrids." However, observations on highly inbred strains selected for specific craniofacial patterns, probably resulting in the fixation of different major genes in each breed, are of questionable relevance to the human situation.

The only observation concerning the effects of inbreeding on occlusal variation has been reported by Schull and Neel.[69] As part of an extensive study of inbreeding effects in Japanese children, they found some suggestion of an increased occurrence of malocclusion in the offspring of consanguineous marriages.

The studies of Chung et al.[13] and Schull and Neel[69] together suggest that inbreeding and outcrossing have either negligible or barely detectable effects on human occlusal variation. Since these two investigations are among the largest and most sophisticated population surveys to consider variables of dental occlusion, further research in this area is unlikely to prove fruitful. The possibility cannot be excluded that, in other populations, genes may be present that would have more significant effects when homozygous or following recombination.

Linkage analysis

Attempts to map autosomes for major genes affecting craniofacial variation have been limited to some preliminary observations on pathological conditions.[41,68] This is to be expected, since the methodology involved in the detection of major genes underlying continuous variation and the linkage of these genes to mapped discrete marker traits represents the forefront of quantitative genetics in the 1970's.[15,34,64]

As applied to dental occlusion, linkage has only been considered in terms of the sex chromosomes. Gorlin, Redman and Shapiro[25] proposed that genes

on the X chromosome cause a lengthening of the mandible relative to the maxilla, and Horowitz and Morishima[35] have confirmed a very high percentage of Class II relationships in XO (Turner's syndrome) subjects. However, Litton et al.[47]and Bookman et al.[7] found no evidence of sex linkage in their studies of Class III malocclusion, so that at this time the question remains unresolved.

Heritability

Studies attempting to partition genetic and environmental components of variation within the craniofacial complex have been more concerned with the facial skeleton[31,36,38,57,58,77] and palatal dimensions[8,67,70] than with occlusal characteristics.

In 1948 Lundstrom[48] analyzed tooth size and dental occlusion in over 200 sets of twins. In an important departure from the methodology and objectives of his predecessors, all characteristics were considered as quantitative continuous variables, so that, for example, the sagittal molar relationship was measured rather than divided into Angle's categories. Lundstrom[50,51] has subsequently suggested that all variables examined had a larger genetic than environmental component of variation.

In a recent report Chung and Niswander[12] have determined the correlations for several characteristics of occlusion in over 1600 pairs of sibs in Hawaii. In comparing their findings with those of Lundstrom it is particularly interesting that in spite of very different sample populations (Hawaii and Sweden) and methods of analysis (sibs and twins), both studies found the same sequence among variables for the relative degree of genetic influence. Of the four characteristics considered by both investigations the degree of genetic determination was greatest for the width of the upper central incisors, and decreased in order for overjet, overbite, and the sagittal molar relationship.

It should be noted that neither a twin analysis nor full sib correlations actually indicate heritability in its most useful form. Determination of the additive genetic variance, or "heritability in the narrow sense," has not been determined for any traits of dental occlusion, although Feldman and Lewontin[19] consider it to be the only type of heritability estimate of use in problems of human genetics.

Population differences

Few workers have attempted to determine the variation in dental occlusion within several populations so that objective evaluations of population differences could be made. For the most part conclusions can only be drawn by comparing the findings of different researchers on single populations. In a recent comprehensive review of the subject Jago[40] emphasized that the only variable common to a sufficient number of studies as to allow such comparisons on a wide basis was Angle's classification of malocclusion. However, this must be undertaken with caution, since Angle's categories are imprecisely defined and subject to considerable interpretation by independent investigators.

Nevertheless, it is clear from these studies that variation among populations does exist. The most interesting genetic difference suggested by the epidemiological data concerns the relatively high frequency of Class II and low frequency of Class III occlusion in North American Caucasian and European populations[1,2,16,24] and the reverse situation (high frequency of Class III, low frequency of Class II) in some groups of Asian origin, including Polynesians,[14] Alaskan Eskimos,[80] Aleuts,[53] American Indians,[20] and Pacific islanders in general.[13] In addition, although environmental effects cannot be excluded, Grewe et al.[28] reported that the

tendency toward Class II relationships in North American Indians increased in relation to the proportion of Caucasian ancestry; Baume[3] has observed a similar effect in Polynesian-Caucasian hybrids.

These observations strongly suggest the presence of quantifiable genetic variation in the sagittal molar relationship among human populations. Specifically, they indicate the possible existence of genes skewing the distribution of molar relationships toward distoclusion in populations of recent European derivation and toward mesioclusion in selected groups with prehistoric origins in Asia.

Populations can be considered to be groups separated by time as well as by geography. Regarding the question of differences among populations in this dimension, there has been some discussion in the orthodontic literature of the effects of evolution and "civilization" on occlusal variation.[44]

Long-term evolutionary changes in the dentofacial complex apparently have involved a reduction in jaw size in association with the needs of cephalization and upright posture. Because we do not have appropriate samples for a valid statistical analysis, the suggestion that there has been an increase in the occurrence of occlusal disharmonies accompanying these changes over the last 50 thousand years or so must remain essentially conjecture. If an increase in occlusal variation has taken place, it could have a genetic basis related to differential selection pressures on the size of the jaws and teeth[71] or to some degree of relaxed natural selection on the facial complex.[59]

A different problem is the observation that an increase in the frequency of occlusal disharmonies seems to occur within one generation after nontechnological societies are introduced to Western culture.[62,66] This change has significant clinical and manpower implications, particularly as these underdeveloped areas increase their demand and need for dental services. However, as discussed by Niswander,[62,63] these changes seem to occur entirely too fast to be associated with genetic selection, and explanations for this observation are more likely to be found in the environment.

Problems and Some Solutions

As noted earlier, genetic questions concerning dental occlusion may be approached at two basic levels. First is the study of populations. Changes in gene frequencies through time within a single population, the maintenance of polymorphisms, and the genetic differences between populations form the core of inquiry for population genetics.

The second level of study is that of individuals within families. This research is concerned with evaluating modes of inheritance, determining linkage, calculating heritability, and detecting major genes. It is also at this level that genetic questions most related to clinical treatment arise.

The purpose of the following discussion is to offer some suggestions regarding the direction for future research on dental occlusion in both of these areas. The distinctions between the two are at times arbitrary, and are maintained here primarily for purposes of organization. Certain methodological problems to be discussed apply to both areas and will therefore be evaluated as they arise.

The concept of malocclusion

Apparent from the preceding review of the literature is the observation that genetic research on dental occlusion has primarily been concerned with the etiology and distribution of "malocclusion." In addition, most studies have considered malocclusion to be largely synonomous with Angle's classification.

There are problems with both aspects of this approach. First, the general concept of malocclusion is inconsistent with modern knowledge of the meaning and basis for variation within populations. The significance of variation among individuals and the present status of genetic theory regarding variation have been well-summarized by Lewontin:[45]

> . . . the essential nature of the Darwinian revolution . . . necessarily takes the variation between individuals as of the essence . . . this emphasis on individual variation as the central reality of the living world is the mark of modern evolutionary thought and distinguishes it from the typological doctrine of previous time.

Implicit in the study of malocclusion, however, is precisely such a typological concept. "Malocclusion" clearly suggests that all variants from a specified normal are abnormal. This approach directs attention away from the analysis of variation among individuals and, in so doing, has delayed insight into the genetics of dental occlusion.

The second aspect of the problem concerns investigations which select as specific objectives for study Angle's Class II or Class III malocclusion. Difficulties arise here when a continuous variable is divided into a small number of ordinal categories which are then treated as a series of independent variables.

Class I, II and III malocclusions are clinically useful but arbitrary divisions of a continuous variable, the sagittal relationship of first permanent molars. For example, although individuals can be grouped as tall, medium or short, and standardized definitions may be adopted, this does not mean that "tallness" should be studied genetically, the appropriate variable is "height." Harris[30] has attempted to justify the study of each of Angle's categories as a separate variable by equating such artificially discontinuous variables with truly discontinuous characteristics. Several other aspects of dental occlusion also vary in a quantitative continuous manner and should be studied as a single unit. Incisor crowding and incisor spacing are continuous, as are posterior buccal crossbite and posterior lingual crossbite.

It may appear that this suggested approach to the measurement of occlusal variation is an oversimplification of a complex problem. Class II and Class III malocclusions are not based simply upon the relationship of first molars, but upon a complex interaction of craniofacial structures. Occlusion may in fact vary depending upon pleiotrophic effects of one or more genes on several components of the craniofacial skeleton and/or soft tissues. However, such relationships would have little bearing on the argument that we need to study occlusal variation rather than malocclusion. Once the interactions are understood in a quantitative manner, multivariate techniques may be applicable for studying several characteristics simultaneously. Nevertheless, occlusion is still related to variation in a series of continuous characteristics and should not be interpreted on the basis of the truncated sampling which occurs when only one tail of the distribution is selected for analysis.

It is also evident that distinct "types" exist within occlusal categories. For example, subjects with Class I molar relationships but with bimaxillary prognathism will have identical measurements of the sagittal molar relationship as individuals with ideal occlusion. This indicates that many variables, in this case the relationship of the maxilla and mandible to the cranial base, need to be examined to determine the extent and nature of variation among individuals in dental occlusion.

Population variation

If epidemiological reports of maloc-

clusion frequencies (except for public health purposes) and genetic studies of Class II and Class III malocclusion are inappropriate objectives for study, what then are appropriate objectives?

First is the relatively simple goal of quantifying and evaluating phenotypic variance. What is needed for this purpose are random samples of diverse human populations. Defining a "population" for a quantitative genetic study can be a problem, the basic concept being that of a group of interbreeding or potentially interbreeding individuals who share a common gene pool. In research on dental occlusion, patients from an orthodontic practice and their families, or all children in a school except those who have had orthodontic treatment are biased and inappropriate samples.

The fundamental question to be evaluated with a valid sample is how much variation actually exists in the population for the characteristics of dental occlusion. This requires a basic descriptive study of overjet, overbite, molar relationship, crossbites, crowding and spacing, malalignment and other occlusal variables, defined in an objective and replicable manner, such that means and variances can be calculated. The role of epidemiological factors such as age, sex, geography, and diet can then be examined to establish their relationship to the observed variation.

After the variation within the population is described and understood, the variation between populations can be compared and the causes for observed differences evaluated. It is at this level that studies of biological distance and discrimination are of particular interest. To the extent that distance matrices based upon different sets of variables are structurally similar to each other and to linguistic, geographic and migrational matrices, insight can be gained into the relative roles of factors which affect population gene frequencies, particularly genetic drift, gene flow, and natural selection.[10,21,22]

Methodological problems

Having suggested that quantitative research is needed on variation in dental occlusion within and among random samples of human populations, it must be acknowledged that such an investigation will be methodologically difficult. One major problem concerns the treatment of subjects with missing teeth. Two questions are related to this problem: first, deciding whether or not to include a given individual, and second, the effects of this decision on the analysis.

After a tooth is lost, drift of adjacent teeth can occur and functional patterns may be altered. As an added environmental effect, this will tend to decrease the correlation between relatives and increase the absolute magnitude of population variation. If longitudinal data are not available to evaluate these changes, measurements can either be recorded directly from the casts, with knowledge that an added environmental component has been included, or a correction can be applied following what must be a somewhat vague judgment as to the effect of the tooth loss. However, when there are only a few remaining teeth, a subject would rarely be included in the analysis. The problem therefore becomes one of selecting a cut-off point, and no generally applicable solution can be offered. The ultimate decision will depend upon the frequency of tooth loss in the sample and the judgment of the investigator.

This decision may have important implications. It is likely that certain occlusal variables are related to early tooth loss. For example, the loss of maxillary incisors due to trauma could be caused by a large overjet. Eliminating these subjects will therefore result in a biased sample selection with a

tendency toward exclusion of extreme values for some variables. This will not only eliminate from study some of the potentially most interesting subjects in terms of a genetic analysis (i.e., those deviating most from the mean), but will also result in lowered estimates of the magnitude of population variation.

A second major problem in population studies concerns subjects in the mixed dentition period. While changes in occlusal variables occur throughout life, once the permanent dentition is reached, age adjustments may be made through the use of regression equations. However, in the mixed dentition period arch dimensions change with the eruption of each permanent tooth.[54] Although the young school-aged subject is frequently the most accessible for research, sample sizes will rarely be large enough to group subjects according to identical patterns of erupted teeth. Some type of compromise will usually have to be accepted. This will affect the calculation of parent-child or sib-sib correlations and the comparison of populations with different age pyramids.

A third and final methodological issue to be discussed concerns the maxillomandibular relationship. There are several potential positions that the mandible may assume while making contact with the maxilla,[65] and a selection from among these will affect the measurement of all interarch characteristics. However, the choices can be realistically reduced to two possible alternatives, centric occlusion (convenience occlusion, habitual occlusion) and centric relation (retruded contact position).

While centric relation is more stable, it is of questionable biological significance. Centric occlusion, although susceptible to change following the loss, movement, or attrition of teeth, is probably the best single position for evaluating biting forces and occlusal function in general. In a word, based upon functional considerations, it is the phenotype. In addition, the difficulties associated with obtaining centric relation in field work and recording it on dental casts has resulted in the general use of centric occlusion by those involved in the development of indices of malocclusion[5,74] and in recent large epidemiologic and genetic studies.[4,13]

In most large collections of dental casts an accurate recording is not available for centric relation or for centric occlusion. A study of dental occlusion in these important collections is only possible by articulating casts in maximum intercuspation. Although this may deviate from an accurate centric occlusion recording for a small number of subjects, it is likely that on a population basis it will not result in significant problems.

Family analysis

While the methods of population genetics and the epidemiology of occlusal variation discussed in the preceding sections can provide information regarding the basis for differences among populations in dental occlusion, orthodontic studies have traditionally been more concerned with problems that require family data for analysis. The issues that have been raised regarding the measurement of continuous variables rather than malocclusion categories do not change for this type of investigation, and the methodological problems of missing teeth, the mixed dentition, and intermaxillary relationships also apply to the following discussion.

Modes of inheritance. The prevailing conventional wisdom is that Class II and Class III malocclusions have a polygenic mode of inheritance, i.e., they are influenced by the action of many genes and environmental effects.[32,33,47,60] This conclusion is based on several ob-

servations: (a) no simple pattern of segregating genes can be established in studies of family pedigrees, (b) craniofacial variation is continuous, and (c) the correlation among relatives for craniofacial variables within occlusal categories conforms to the expectations of polygenic inheritance. However, if the variation is continuous, why have subjects been grouped as only present or absent for the characteristic of interest and, in addition, if evaluating the similarity among relatives, why not directly measure the occlusal relationship and determine its correlations? Considering the variable of interest to be the sagittal molar relationship rather than the presence or absence of Class II and Class III categories makes these suggestions self-evident.

In any case, while we agree that occlusal variables are most likely polygenic, such a conclusion is unwarranted by the data that have been presented so far.[32,33,47] There are two reasons for the frequent misinterpretation of the available data: (a) insufficient consideration of the possible role of environmental effects, and (b) the question of the meaning of polygenic inheritance when it has, in fact, been demonstrated to exist.

Perhaps the most questionable simplifying assumption in the many genetic models used to evaluate modes of inheritance is the hypothesized lack of environmental covariation among relatives. Not to be confused with Lamarkian genetics, aspects of environmental covariation are in fact being developed into a concept of cultural inheritance by Cavalli-Sforza and Feldman.[11] The problem is that related individuals clearly have more similar environments than the population as a whole. For characteristics that are phenotypically plastic, i.e., affected by various environmental influences, relatives can be similar because of common environments rather than common genes. It is also well-established that a trait can be continuously distributed with only a single segregating gene if there are environmental effects.[76] Such single gene traits would correlate among relatives according to the degree of common environment, which is generally similar to the percentage of common genes, and would show no clear segregational patterns in pedigree studies. Because of the very real possibility of environmental effects, there is no justification in concluding from the available literature that occlusal variables are polygenic. We agree that a polygenic mode is most reasonable, and the weight of evidence presented to date is supportive of it. However, the data are not inconsistent with environmentally-sensitive single gene inheritance, and a valid distinction between the two models has not been presented for any craniofacial variables.

Major genes. If occlusal variables were demonstrated to be polygenic, what would this finding most likely mean? The assumptions of biometrical genetics require a sufficiently large number of genes to have a continuous distribution of effects. While numbers are rarely discussed, the "ball-park" estimates of many investigators would probably range from 25 to 200, since typical figures are 35 loci for the weight of mice at six weeks of age, and 99 for the number of abdominal bristles in Drosophila.[17]

With this many loci affecting a variable, what would be the next worthwhile research effort? Individual gene effects cannot be detected, so all that remains is establishing the heritability of the characteristic. (How much of the variation can be attributed to genetic causes?) However, while this knowledge can be of interest for several problems of evolutionary biology, it is of little consequence to any clinical decisions.[19]

The degree of heritability has little if any bearing on how successful clinical procedures will be. Contrary to common opinion, the extent to which genes determine a trait has no relationship whatsoever with the success of environmental intervention.[18,46,55] In addition, it will have no bearing on the type of treatment, nor will it be of much use in genetic counseling. For the specific orthodontic problem of predicting growth changes, the value of variables can be determined without any reference to their heritability.

Beyond these issues, Lewontin[46] and Feldman and Lewontin[19] have raised important questions about the validity of linear models for the partitioning of variance components. While debate on this problem continues,[56] it is important to point out that the manner in which genotype-environment interactions change in their effect on the phenotype over the range of environments and genotypes (their "norm of reaction") may mean that the whole effort has been "the endless search for better methods of estimating useless quantities."[46]

If, therefore, occlusal variation was demonstrated to be polygenic, and this meant large numbers of segregating genes, there would be little of value that genetics could contribute to clinical orthodontics, except in the area of severe chromosomal anomalies.

Fortunately, this is probably not the case. Whenever the number of genes affecting polygenic traits has actually been determined, a remarkably small number have been found.[76] The biometric estimate of 99 loci for abdominal bristle number in Drosophila is in actuality five loci accounting for 85% of the difference between high and low lines.[75] Human skin color seems to be controlled by only 3 or 4 loci.[61,72] As discussed by Thompson,[76] this lower number of genes is much more compatible with estimates of the total number in the genome. Furthermore, these genes are not all of equal significance. This raises the possibility, which Thoday[75] emphasized as the next major goal for human genetics, of locating and studying genes within the normal range of continuous variation.

Until recently major genes (single genes whose effects could be observed phenotypically) were considered to be of two types, pathological and polymorphic.[75] The pathological referred to extreme deviants (e.g., achondroplasia) and the polymorphic to distinct normal categories (e.g., the ABO blood cell antigens). Recently a new type of major gene has been recognized, but can only be "seen" by the computer in a statistical analysis. These are genes with large effects within the normal range of variation, and efforts by a number of investigators now make it possible to detect the presence of such genes by segregation and linkage analysis.[15,34,64]

As Lewontin[46] has suggested, it is possible that clinical treatment will vary depending upon alternative causes for a disorder. (This is a different problem than the relative contributions of an interacting genotype and environment, i.e., heritability.) Pathological major genes may act as a locus independent of the segregating genes normally affecting the variation of a character. In this sense a single gene "overrides the system" and produces an effect regardless (or greatly modifying) of what has been inherited by the polygenic system. The study of extreme variants, particularly if related to single genes, is the one circumstance noted earlier in which a typological study of Class II or Class III occlusion would be appropriate. However, the response need not be so dramatic as to produce only extreme manifestations.[63] It is possible that many strong familial similari-

ties are due to single major genes running in a family but not widely distributed in the population. Therefore, the possibility of establishing different causes exists within the range of normal variation as well as for the occurrence of extreme phenotypes.

In summary, it is suggested that there is the possibility of detecting two types of major genes underlying continuous variation. First are alleles with large effects at loci which normally segregate for a characteristic, and second would be a gene at a single pathological (or "familial") locus but producing an effect within the normal range of variation. Although application will not be in the immediate future, detection of these genes holds the promise of substantial contributions to clinical practice. Once major genes are located, their biochemical products can be studied. These data may ultimately be of use in accurate predictions of long-term growth changes and direct biochemical methods for clinical intervention.

It may seem that such objectives are highly speculative; particularly if it should be found that anatomical variation is based more upon regulatory gene control at the transcriptional level than upon differences in structural proteins, success in controlling and predicting occlusal variation will be in the more distant future. At the very least, however, a rationale has been developed with a long-range goal of contributing to the direct solution of clinical problems. No more, and perhaps less, has been achieved over the past 50 years.

Summary and Conclusions

Research on the genetics of dental occlusion has traditionally been based upon the concept of "malocclusion." Although of recognized clinical value, the biological validity of the various categories of malocclusion is questionable. Genetic research should instead center upon concepts related to continuous variables and population variation.

The magnitude of variation for the characteristics of dental occlusion needs to be quantified within diverse human populations. The relationship of this variation to epidemiological factors and the nature of differences among populations are also areas in need of much investigation.

This type of research will face methodological problems not encountered in studies of malocclusion. Measurements taken on subjects with missing teeth provide a potential source of bias that must be carefully evaluated, since these subjects cannot simply be excluded from study without resulting in an alternative type of bias. The potential intermaxillary relationships appropriate for study are centric relation and centric occlusion. While centric relation has an advantage in stability, it is suggested that centric occlusion (convenience occlusion) is the functional phenotype and therefore the most appropriate position from which to take measurements.

Several recent studies stress a polygenic mode of inheritance for the characteristics of dental occlusion. The evidence is reviewed and evaluated, and it is concluded that, although a polygenic mode is most likely, there are insufficient data to exclude the possibility of environmentally-sensitive single gene inheritance.

If occlusion is demonstrated to be polygenic, studies attempting to partition environmental and genetic causes of variance will contribute little to clinical problems. Long-term objectives should instead center upon the detection of major genes and determination of their biochemical action.

Department of Orthodontics
School of Dental Medicine
University of Connecticut
Farmington, Connecticut 06032

ACKNOWLEDGMENTS

We thank Dr. Jerry Niswander, Human Genetics Branch, NIDR, and Drs. Donald Kolakowski, Andrew Poole and Sam Weinstein, University of Connecticut School of Dental Medicine, for their helpful comments on various drafts of this manuscript.

This research was supported by United States Public Health Service Grants DE 00136 and DE 03729 from the National Institute of Dental Research, National Institutes of Health, Bethesda, Md.

REFERENCES

1. Adler, P.: The incidence of dental caries in adolescents with different occlusions. *J. Dent. Res.*, 35:344-349, 1956.
2. Ast, D. B., Carlos, J. P. and Cons, N. C.: The prevalence and characteristics of malocclusion among senior high school students in upstate New York. *Am. J. Orthodont.*, 51: 437-445, 1965.
3. Baume, L. J.: Uniform methods for the epidemiologic assessment of malocclusion. Results obtained with the World Health Organization standard methods (1962 and 1971) in South Pacific populations. *Am. J. Orthodont.*, 66:251-272, 1974.
4. Baume, L. J. and Marechaux, S. C.: Uniform methods for the epidemiologic assessment of malocclusion. *Am. J. Orthodont.*, 66:121-129, 1974.
5. Baume, L. J., Horowitz, H. S., Summers, C. J., Backer Dirks, O., Brown, W. A. B., Carlos, J. P., Cohen, L. K., Freer, R. J., Harvold, E. P., Moorrees, C. F. A., Salzmann, J. A., Schmuth, G., Solow, B. and Taatz, H.: A method for measuring occlusal traits. *Int. Dent. J.*, 23:530-537, 1973.
6. Björk, A.: Some biological aspects of prognathism and occlusion of the teeth. *Acta. Odont. Scand.*, 9:1-40, 1950.
7. Bookman, D. J., DeMuth, D. L., Dulaney, H. L., George, D. C., Haller, E. L., Marconi, F. I., Massignan, D. E., Trojan, T. M. and Vedder, J. L.: *Inheritance of the Craniofacial Complex in Class III Malocclusion.* Unpublished Master's thesis, University of Michigan, 1974.
8. Bowden, D. E. J. and Goose, D. H.: The inheritance of palatal arch width in human families. *Arch. Oral Biol.*, 13:1293-1295, 1968.
9. Brash, J. C., McKeag, H. T. A. and Scott, J. H.: *The Aetiology of Irregularity and Malocclusion of the Teeth*, 2nd Ed. London, Dental Board of the United Kingdom, 1956.
10. Brewer-Carias, C. A., LeBlanc, S. and Neel, J. V.: Genetic structure of a tribal population, the Yanomama Indians. XIII. Dental microdifferentiation. *Am. J. Phys. Anthrop.*, 44: 5-14, 1976.
11. Cavalli-Sforza, L. L. and Feldman, M. W.: Cultural versus biological inheritance: phenotypic transmission from parents to children (a theory of the effect of parental phenotypes on children's phenotypes). *Am. J. Hum. Genet.*, 25:618-637, 1973.
12. Chung, C. S. and Niswander, J. D.: Genetic and epidemiologic studies of oral characteristics in Hawaii's schoolchildren. V. Sibling correlations in occlusion traits. *J. Dent. Res.*, 54:324-329, 1975.
13. Chung, C. S., Niswander, J. D., Runck, D. W., Bilben, S. E. and Kau, M. C. W.: Genetic and epidemiologic studies of oral characteristics in Hawaii's schoolchildren. II. Malocclusion. *Am. J. Hum. Genet.*, 23:471-495, 1971.
14. Davies, G. N.: Dental conditions among the Polynesians of Pukapuka (Danger Island). I. General background and the prevalence of malocclusion. *J. Dent. Res.*, 35:115-131, 1956.
15. Elston, R. C. and Stewart, J.: A general model for the genetic analysis of pedigree data. *Human Hered.*, 21:523-542, 1971.
16. Emrich, R. E., Brodie, A. G. and Blayney, J. R.: Prevalence of Class I, Class II and Class III malocclusions (Angle) in an urban population. An epidemiological study. *J. Dent. Res.*, 44:947-953, 1965.
17. Falconer, D. S.: *Introduction to Quantitative Genetics.* New York, Ronald Press, 1960.
18. ———: The inheritance of liability to certain diseases, estimated from the incidence among relatives. *Ann. Hum. Genet.*, 29:51-76, 1965.
19. Feldman, M. W. and Lewontin, R. C.: The heritability hang-up. *Science*, 190:1163-1168, 1975.
20. Foster, L. W.: Dental conditions in White and Indian children of Northern Wisconsin. *J. Am. Dent. Assoc.*, 29:2251-2255, 1942.
21. Friedlaender, J. S., Sgaramella-Zonta, L. A., Kidd, K. K., Lai, L. Y. C., Clark, P. and Walsh, R. J.: Biological divergences in South-Central Bougainville: An analysis of blood polymorphism gene frequencies and anthropometric measurements utilizing tree models, and a comparison of these variables with linguistic, geographic and migrational "distances." *Am. J. Hum. Genet.*, 23: 253-270, 1971.

22. Friedlaender, J. S.: *Patterns of Human Variation. The Demography, Genetics and Phenetics of Bougainville Islanders.* Cambridge, Harvard Univ. Press, 1975.
23. Goodman, H. O.: Genetic parameters of dentofacial development. *J. Dent. Res.*, 44:174-184, 1965.
24. Goose, D. H., Thomson, D. G. and Winter, F. C.: Malocclusion in school children of the West Midlands (England). *Brit. Dent. J.*, 102:174-178, 1957.
25. Gorlin, R. J., Redman, R. S. and Shapiro, B. L.: Effect of X-chromosome aneuploidy on jaw growth. *J. Dent. Res.*, 44:269-282, 1965.
26. Graber, T. M.: *Orthodontics. Principles and Practice,* 2nd Ed. Philadelphia, W. B. Saunders Co., 1966.
27. Gregory, K. E., Koch, R. M. and Swiger, L. A.: Malocclusion—a hereditary defect in cattle. *J. Hered.*, 53:168-170, 1962.
28. Grewe, J. M., Cervenka, J., Shapiro, B. L. and Witkop, C. J. Jr.: Prevalence of malocclusion in Chippewa Indian children. *J. Dent. Res.* 47: 302-305, 1968.
29. Gruneberg, H. and Lea, A. J.: An inherited jaw anomaly in long-haired dachshunds. *J. Genet.*, 39:285-296, 1940.
30. Harris, J. E.: Problems in the statistical inspection of cranio-facial variables during growth and development. In Moyers, R. E. and Krogman, W. M. (eds.): *Craniofacial Growth in Man.* Oxford, Pergamon Press, 1971.
31. Harris, J. E., Kowalski, C. J. and Watnick, S. S.: Genetic factors in the shape of the craniofacial complex. *Angle Orthodont.*, 43:107-111, 1973.
32. Harris, J. E., Kowalski, C. J. and Walker, S. J.: Intrafamilial dentofacial associations for Class II Division 1 probands. *Am. J. Orthodont.*, 67:563-570, 1975.
33. ———: Dentofacial differences between "normal" sibs of Class II and Class III patients. *Angle Orthodont.*, 45:103-107, 1975.
34. Haseman, J. K. and Elston, R. C.: The investigation of linkage between a quantitative trait and a marker locus. *Behav. Genet.*, 2:3-19, 1972.
35. Horowitz, S. L. and Morishima, A.: Palatal abnormalities in the syndrome of gonadal dysgenesis and its variants and in Noonan's syndrome. *Oral Surg.*, 38:839-844, 1974.
36. Horowitz, S. L., Osborne, R. H. and DeGeorge, F. V.: A cephalometric study of craniofacial variation in adult twins. *Angle Orthodont.*, 30: 1-5, 1960.
37. Hunt, E. E., Jr.: Malocclusion and civilization. *Am. J. Orthodont.*, 47: 406-422, 1961.
38. Hunter, W. S.: A study of the inheritance of craniofacial characteristics as seen in lateral cephalograms of 72 like-sexed twins. *Trans. Europ. Orthodont. Soc.*, 41:55-70, 1965.
39. Isaacson, R. J., Christiansen, R. L., Evans, C. A. and Riedel, R. A.: Research on variation in dental occlusion. *Am. J. Orthodont.*, 68:241-255, 1975.
40. Jago, J. D.: The epidemiology of dental occlusion; a critical appraisal. *J. Pub. Health Dent.*, 34:80-93, 1974.
41. Krogman, W. M.: The role of genetic factors in the human face, jaws and teeth: a review. *Eugen. Rev.*, 59:165-192, 1967.
42. ———: Craniofacial growth and development: an appraisal. *Yrbk. Phys. Anthrop.*, 18:31-64, 1974.
43. Lavelle, C. L. B.: Maxillary and mandibular tooth size in different racial groups and in different occlusal categories. *Am. J. Orthodont.*, 61:29-37, 1972.
44. ———: A study of multiracial malocclusions. *Community Dent. Oral Epidemiol.*, 4:38-41, 1976.
45. Lewontin, R. C.: *The Genetic Basis of Evolutionary Change.* New York, Columbia Univ. Press, 1974.
46. ———: The analysis of variance and the analysis of causes. *Am. J. Hum. Genet.*, 26:400-411, 1974.
47. Litton, S. F., Ackerman, L. V., Isaacson, R. J. and Shapiro, B. L.: A genetic study of Class III malocclusion. *Am. J. Orthodont.*, 58:565-577, 1970.
48. Lundstrom, A.: *Tooth Size and Occlusion in Twins.* New York, S. Karger, 1948.
49. ———: The aetiology of crowding of teeth (based on studies of twins and from morphological investigations) and its bearing on orthodontic treatment. *Trans. Europ. Orthodont. Soc.*, 176-191, 1951.
50. ———: The significance of genetic and nongenetic factors in the profile of the facial skeleton. *Am. J. Orthodont.*, 41:910-916, 1955.
51. ———: Aetiology and prevention of malocclusion. In Lundstrom, A. (ed.), *Introduction to Orthodontics.* New York, McGraw-Hill Book Co., 1960.
52. Moorrees, C. F. A.: The dentition as a criterion of race with special reference to the Aleut. *J. Dent. Res.*, 30:815-821, 1951.
53. ———: *The Aleut Dentition.* Cambridge, Harvard Univ. Press, 1957.

54. ———: *The Dentition of the Growing Child.* Cambridge, Harvard Univ. Press, 1959.
55. Morton, N. E.: Analysis of family resemblance. I. Introduction. *Am. J. Hum. Genet.*, 26:318-330, 1974.
56. ———: Analysis of family resemblance and group differences. *Soc. Biol.*, 22:111-116, 1975.
57. Nakata, M., Yu, P. L. and Nance, W. E.: Multivariate analysis of craniofacial measurements in twin and family data. *Am. J. Phys. Anthrop.*, 41:423-430, 1974.
58. Nakata, M., Yu, P. L., Davis, B. and Nance, W. E.: Genetic determinants of craniofacial morphology: a twin study. *Ann. Hum. Genet.*, 37:431-443, 1974.
59. Neel, J. V. and Salzano, F. M.: Further studies on the Xavante Indians. X. Some hypotheses-generalizations resulting from these studies. *Am. J. Hum. Genet.*, 19:554-574, 1967.
60. Nelson, M. M.: A brief study of the genetics of malocclusion. *Trans. Europ. Orthodont. Soc.*, 55-68, 1969.
61. Nicholls, E. M.: Pigment spotting in man and the number of genes determining skin and eye color. *Human Hered.*, 23:1-12, 1973.
62. Niswander, J. D.: Further studies on the Xavante Indians. VII. The oral status of the Xavantes of Simeos Lopes. *Am. J. Hum. Genet.*, 19: 543-553, 1967.
63. ———: Genetics of common dental disorders. *Dent. Clin. N.A.*, 19:197-206, 1975.
64. Ott, J.: Estimation of the recombination fraction in human pedigrees: efficient computation of the likelihood for human linkage studies. *Am. J. Hum. Genet.*, 26:588-597, 1974.
65. Posselt, U.: *The Physiology of Occlusion and Rehabilitation,* 2nd Ed. Philadelphia, F. A. Davis Co., 1968.
66. Price, W. A.: Studies of relationships between nutritional deficiencies and (a) facial and dental arch deformities and (b) loss of immunity to dental caries among South Sea Islanders and Florida Indians. *Dent. Cosmos,* 77:1033-1045, 1935.
67. Riquilme, A. and Green, L. J.: Palatal width, height and length in human twins. *Angle Orthodont.,* 40:71-79, 1970.
68. Salzmann, J. A.: Effect of molecular genetics and genetic engineering on the practice of orthodontics. *Am. J. Orthodont.*, 61:437-472, 1972.
69. Schull, W. J. and Neel, J. V.: *The Effects of Inbreeding on Japanese Children.* New York, Harper and Row, 1965.
70. Shapiro, B. L.: A twin study of palatal dimensions partitioning genetic and environmental contributions to variability. *Angle Orthodont.,* 39: 139-151, 1969.
71. Sofaer, J. A., Bailit, H. L. and MacLean, C. J.: A developmental basis for differential tooth reduction during hominid evolution. *Evolution,* 25: 509-517, 1971.
72. Stern, C.: Model estimates of the number of gene pairs involved in pigmentation variability of the Negro-American. *Human Hered.,* 20: 165-168, 1970.
73. Stockard, C. R. and Johnson, A. L.: *The Genetic and Endocrinic Basis for Differences in Form and Behavior.* Philadelphia, Wistar Institute, 1941.
74. Summers, C. J.: The occlusal index: a system for identifying and scoring occlusal disorders. *Am. J. Orthodont.* 59:552-567, 1971.
75. Thoday, J. M.: New insights into continuous variation. In *Proc. 3rd Int. Cong. Hum. Genet.* Baltimore, Johns Hopkins Press, 1967.
76. Thompson, J. N. Jr.: Quantitative variation and gene number. *Nature,* 258:665-668, 1975.
77. Watnick, S. S.: Inheritance of craniofacial morphology. *Angle Orthodont.*, 42:339-351, 1972.
78. Weinberger, B. W.: *Orthodontics. An Historical Review of its Origin and Evolution.* St. Louis, C. V. Mosby, 1926.
79. Wiener, G. and Gardner, W. J. F.: Dental occlusion in young bulls of different breeds. *Anim. Prod.*, 12:7-12, 1970.
80. Wood, B. F.: Malocclusion in the modern Alaskan Eskimo. *Am. J. Orthodont.*, 60:344-354, 1971.