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POSTNATAL RISK.

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ROBERT DIBENNARDO

1973

**PRENATAL STRESS, DEVELOPMENTAL 'NOISE,' AND
POSTNATAL RISK**

by

ROBERT DIBENNARDO

**A dissertation submitted to the Graduate
Faculty in Anthropology in partial fulfillment of
of the requirements for the degree of Doctor
of Philosophy, the City University of New York.**

1973

This manuscript has been read and accepted for the Graduate Faculty in Anthropology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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Chapter I

Introduction

The aim of the present study is to add to the growing body of evidence pointing to the important potentials of investigations on the plasticity of the human dentition. 'Plasticity' is here defined as the degree of variation possible in growth and development when the individual genetic endowments in a population are modified by different environments. Since it is only the genetic component of the phenotype that is differentially transmissible between generations, the importance of genotype-environment interactions have, in general, been minimized in the attempt to dichotomize the phenotype into separable genetic and environmental components. The regrettable practical consequence of this practice in the area of dental research has been the assumption that the utility of the teeth in evolutionary or population studies rests on that part of their size or shape determined by the genes.

Waddington in particular has emphasized the importance of adaptability in the organism to the adaptation

of the population (1957). Demonstrating that the remarkable uniformity of phenotype for characteristics assumed to be strongly associated with fitness need not be the result of underlying genetic uniformity (1953), he introduced the concept of the 'canalized' phenotype. According to Waddington, the developmental events which lead to canalization function to make the expression of the phenotype homogeneous over a wide range of underlying genotypes for some optimum value determined by the adaptive needs of the population.

Under certain conditions of development the 'canalizing' or 'buffering' system of the organism can be unsettled to the point where it is inoperative and the underlying genetic variability finds expression in increased phenotypic variability. However, only a substantial environmental or genetic insult can cause the canalized phenotype to deviate from its final or mature form. In this study, we hope to identify the stresses which disrupt this developmental homeostasis in the human dentition.

In 1953, Mather proposed that the random or 'fluctuating asymmetry' of homologous paired structures in bilaterally symmetrical organisms be used as a measure of developmental homeostasis. In such organisms the expression of the character on the two sides should be a function of

identical developmental processes with symmetry the norm. Asymmetry is thus a measure of the 'noise' or interference encountered by the organism in the attempt to render the same developmental messages twice. The degree of this noise or interference is assumed to be proportional to the magnitude of local disturbances in the course of development of the particular structure under study. However the susceptibility to such interference is determined by the 'genetic architecture' of the genotype. Genotypes which can resist such interferences are thus better buffered against the stresses of development and can be considered more stable.

Tests of this hypothesis in infrahuman organisms and plants tend to confirm the relationship between the genetic stresses of inbreeding, continued selection and environmental stress, and degree of asymmetry. In addition there have been several successful attempts to associate genetic and environmental stresses in man with asymmetry of the teeth (see chapter 2). Though few in number, the human studies suggest the possibility that asymmetry may prove a valuable measure of both relative population fitness and the general level of risk for individuals within populations.

Our aims in this study are 1) to identify the sources of stress on the developing dentition and their relationship to asymmetry, and 2) to explore the associations between

asymmetry and risk for individuals within our sample. In this introductory chapter, we shall briefly outline the conceptual framework for our analysis.

Our primary assumption is that fluctuating asymmetry is a measure of the developmental stability of the organism. The arguments and evidence supporting and challenging this contention are reviewed in chapter 2. The dentition is the organ system of choice in the study of asymmetry because teeth can be easily measured, especially from dental casts. Teeth or casts are available not only on contemporary human beings, but are uniquely abundant in the fossil record. Consequently, the teeth have a disproportionately great value to the developmental biologists, as well as the evolutionist.

The further assumption that teeth can reflect environmental stresses is reviewed in chapter 3 in an attempt to delineate the specific kinds of stress effective in this respect, to quantify the limits of this susceptibility, and to determine the critical period of susceptibility for the developing teeth. As a consequence of this review, we conclude that the dentition is detectably influenced by environmental factors, and more specifically, by non-genetic maternal influences operating during the perinatal phase of growth when the teeth are beginning to form.

In chapter 4, we strive to define stress in terms of the conclusions arrived at above. Birth weight and fetal growth rate are discussed as the most important measures of the adequacy of the maternal environment and hence as the primary measure of stress on the dentition. Chapter 5 pursues this idea by examining the specific aspects of the maternal environment which affect birth weight and fetal growth rate, and Chapter 6 considers the possibility of long term sequelae to prenatal stress, especially with regard to morbid risk. If it can be shown that risk is a function of the same stresses which lead to asymmetry, then it is possible that asymmetry can be used as an index of risk.

The remaining chapters contain the substance of our analysis, chapter 7 dealing with methodological problems, and the remaining chapters reporting the results of the inquiry.

Summary

Briefly stated our hypothesis is that the perinatal stresses associated with a poor maternal environment renders the developing teeth susceptible to fluctuating asymmetry. The level of asymmetry is a function of both the degree of stress and the stabilizing capacity of the genotype. To the degree that susceptible individuals are also

susceptible to postnatal morbid risk, asymmetry may emerge as an index of individual risk. The aim of our analysis is to quantify the associations postulated to determine whether or not this hypothesis is tenable.

Chapter 2

Fluctuating Asymmetry as a Measure of Developmental Stability

The theoretical formulations underlying the study of asymmetry have been extensively explored by Mather who first suggested (1953) that bilateral asymmetry might be a useful measure of developmental stability. The purpose of this chapter is to review the experimental evidence testing this hypothesis, and by contrasting the promise and limitations revealed by the available literature, justify the goals of the present study.

Theory

According to Mather wild type strains show greater phenotypic uniformity for various characteristics than do mutants. The eyeless mutation in *Drosophila*, for example, is more variable between individuals and between sides of the same individual, than the wild type phenotype. From embryological evidence he reasons that the genotype is not only adjusted to build up the initial differences in the cell which lead to differentiation, but that it is also

adapted to suppressing the same kind of differences where their effects would be inappropriate. Presumably mutation disrupts this adjustive capacity by setting up new circumstances of development which unbalance the overall stability of the interacting parts of the genotype. Failure of the two sides to develop identically in bilaterally symmetrical organisms reflects this instability and therefore "the study of asymmetry affords a means of investigating the genotypic stabilization of developmental processes" (1953: 299).

In Mather's model, both sides of the individual are assumed to be under identical genetic control. The expression of the character will be symmetrical barring local disturbances which might affect one or the other side at random. This kind of random difference between sides has subsequently been referred to as fluctuating asymmetry by Van Valen (1962) and any particular individual will exhibit fluctuating asymmetry in proportion to the degree of the local disturbance and the capacity of his genotype to suppress it.

Experiments

A. Drosophila

Using his theoretical model, Mather studied the

asymmetry of chaeta number in Oregon and Samarkand strains of Drosophila (1953). The left-right variance in pure bred parents and F_1 and F_2 hybrids indicated clearcut differences in the stabilizing powers of different genotypes. The results of inbreeding studies showed that differences between the sides were more variable in the Oregon and Samarkand inbred lines than in the F_1 's and F_2 's of their crosses. Two selection experiments started from the same cross confirmed the genetic control of stability by establishing differences between lines selected for high or low expression of asymmetry.

Thoday (1958), also working with sternopleural chaeta number in Drosophila, found that after 10 generations of selection for high or low chaeta number a marked degree of deterioration of developmental stability was demonstrable in the selected lines as measured by degree of bilateral asymmetry. He attributes this deterioration to the unbalancing of linked gene complexes associated with the selected trait. Lerner's hypothesis that genetic instability is attributable to increasing homozygosity (1954) is discounted by Thoday, since the same deterioration of stability was observed in crosses between the selected lines.-

Beardmore (1968) also using the assumption that

asymmetry measures developmental stability studied the asymmetry of chaeta number of inbred lines, their F_1 hybrids, and wild strains, in thermally constant and diurnally fluctuating temperatures (20° / 30°C). As per Mather (1953) he found that in constant temperature the homeostasis of the F_1 hybrids was greater than that of the inbred lines. In fluctuating temperatures, however, the F_1 's appear to be no more homeostatic (i.e. symmetrical) than the inbreds, but were significantly more viable. Wild strains exhibited less asymmetry under fluctuating than under constant temperature but lose this capacity after being bred for 15 generations in a laboratory under constant conditions. Beardmore argues that the genetic architecture buffering against fluctuating temperature in the wild is a product of natural selection, and is lost after breeding under laboratory conditions.

On the negative side, Reeve (1960) takes exception to what he claims is an implicit notion in the statements of Mather and Thoday--namely that the genetic structure of stability will affect all characters, so that any bilateral character we study will give the same measure of the stabilizing capacity of the genotype. In selection experiments on wild stocks of Drosophila, Reeve was able both to increase or decrease bilateral asymmetry of sternopleurals. Since

asymmetry was reduced well below the level of wild stocks
he concludes

either that the (-) selected lines in these experiments have a much greater developmental homeostasis than the wild stock or F_2 from which they originated, or that the level of asymmetry is not a measure of developmental homeostasis. The first of these conclusions defies common sense--a wild stock must surely be maintained at or near the maximum level of homeostasis by natural selection and we are forced to conclude that the level of sterno-pneural asymmetry does not give us an adequate index of homeostasis, in so far as this is a general characteristic of the organism. (p. 167)

Further evidence of the lack of any general component of buffering can be seen in the work of Van Valen (1962). In this study the fluctuating asymmetry of different traits was examined in three different species. These included chaeta and wing characteristics of Drosophila melanogaster, various aspects of the cheek teeth of Peromyscus leucopus, and aspects of the cheek teeth of Griphippus gratus, a fossil horse. A test for a mean positive correlation in asymmetry between a number of unrelated traits in the same individual was made on the assumption that this would indicate both a general buffering capacity and phenotypic variation in this buffering capacity. The mean correlation for Drosophila and Peromyscus, however, was found to be zero, and the small correlation of 0.046 in

Griphippus was discounted. The evidence would therefore argue against any general organism wide buffering component.

B. Plants and Animals

The same concepts used in the study of developmental stability in *Drosophila* have been applied in the analysis of the developmental relations among some quantitative characters in the rice plant by Sakai and Shimamoto (1965). They postulate that if instability is the outcome of errors or 'noise' during the developmental process, then closely related characters would show more or less similar degrees of instability. These authors postulate a gene set whose pleiotropic effects control several characteristics in rice plants on the basis of genetic intercorrelations. Fairly high intercorrelations were found between the same characteristics with respect to similarity of instability (i.e. asymmetry). These data tend to support the notion that a single gene set had been isolated in this plant species.

For the common house mouse, Bader (1965) investigated 19 populations compared with respect to fluctuating asymmetry in the width (i.e. bucco-lingual diameter) of the three molar teeth. There were 5 wild populations, 5 random-bred laboratory populations, 7 inbred and 2 hybrid groups.

Among the two measures of asymmetry used was the product moment correlation between antimeres. For this measure, the two genetically variable populations (wild and random-bred) showed a significantly higher mean coefficient of correlation than the two genetically uniform groups. Also of importance was the significant difference between inbred and hybrid strains for M_3 where the hybrids are considerably more symmetrical than the inbreds. Examination of the intraindividual variance of the inbred and hybrid populations supports the contention that the lesser total variance in hybrid strains is due, in part, to a reduction of the intra-individual component (i.e. reduction in asymmetry). As in Van Valen's study of fossil horse dentition, Bader found no indication of a system wide concordant level of dental asymmetry for a given individual.

C. Asymmetry in Man

The first of the three developmental studies of asymmetry in man is that of Niswander and Chung (1965). In examining the effects of inbreeding on tooth variability in Japanese children, they considered intra-individual variation in terms of asymmetry as well. The within pair variance of right vs. left central incisors for children of unrelated, second cousin, 1-1/2 cousin, and 1st cousin matings were compared in males and females. There was a

slight tendency for this variance to increase with F (coefficient of consanguinity), with an especially high value for the 1-1/2 cousin group. A regression analysis of asymmetry against F , F^2 , and SES (socio-economic status) confirmed a significant curvilinear association between asymmetry and F , and with regard to the non-conformity of 1-1/2 cousins, the authors speculated that it is perhaps significant that these matings are cross generation in the genetic sense and hence somewhat unusual. They do not, however, elaborate on this point.

Adams and Niswander (1967) studied the palm prints and dental casts of individuals over 5 years of age participating in a study of oral clefts at the Lancaster Cleft Palate Clinic, Lancaster, Pennsylvania. Individuals from their 88 families with cleft histories and 82 families with no such histories, were divided into those with familial cleft lip[†] cleft palate, sporadic cleft lip[†] cleft palate, or sporadic isolated cleft palate, and then compared to a group of children attending the clinic for reasons not associated with oral clefts. There was a significant difference in the intra-pair variance with respect to the palmar dermatoglyphics and the bucco-lingual diameter of the first lower molar between the familial cleft lip[†] cleft palate group and the controls. The authors postulate a

polygenic predisposition for this phenomena based upon a threshold effect where the substitution of deleterious genes in polygenic systems buffering the development of the organism lowers the level of buffering beyond a point where it can compensate for environmental disturbances. This incapacity is manifested both as cleft lip $\pm$ cleft palate and increased dermatoglyphic and dental asymmetry. The further implication, though never explicitly stated, is that asymmetry reflects an organism wide buffering component affecting organ systems as diverse as the dentition and dermatoglyphic patterns. Alternatively it could imply a developmental relationship (e.g. in terms of common time of development or pleiotropy) between these two systems.

Finally Bailit et al. (1970) made a comparison of the degree of dental asymmetry among four populations subject to varying genetic and environmental stresses. On the basis of ethnographic and medical data a population of Tristanites, of Kwaio, of Nasioi, and of Boston children were ranked as most to least stressed respectively. Mesiodistal diameters of all the permanent teeth except the third molars were measured from casts for each of the four populations. The intra-class correlation coefficient (r) between n pairs of homologous teeth for each individual was made for all cases where $n \geq 9$. The r values were then

transformed into Fisher's z values and then averaged within each population. The differences in mean asymmetry within each population were as predicted from the rank order on ethnographic and medical grounds, and the mean differences were statistically significant at the 0.01 level.

Implicit in the methodology followed above is the notion that buffering ability is at least organ-system-wide, so that asymmetry in the dentition as a whole can be pooled to give a dental asymmetry score for any given individual. In view of the work of Reeves, Van Valen, and Bader mentioned above, such an assumption seems tenuous, but the four populations were also compared on a tooth by tooth basis with essentially the same results.

An important negative finding was revealed in the Tristanites. Extensive pedigrees were available for this population, from which individual coefficients of consanguinity were calculated. In the Tristanites, no demonstrable linear association occurred between consanguinity and dental asymmetry.

Summary and Conclusions

The evidence from *Drosophila* experiments indicates that the level of asymmetry varies with strain, is higher in inbred than hybrid groups, is subject to natural selection,

and varies under different environmental circumstances. Furthermore, there is no evidence for an organism-wide general buffering capacity.

One or more of these relationships which hold for *Drosophila* have been demonstrated in organisms as diverse as plants, rodents, and man, so that in summary we may make the following points:

(a) In infra-human organisms the level of asymmetry seems related to the genetic stress of inbreeding, though it has not been possible to specify what aspect of inbreeding produces the stress. Thoday favors the 'unbalancing of gene complexes' theory to Lerner's notion that increasing homozygosity is the important factor, but these viewpoints are not necessarily mutually exclusive. Inbreeding stress in man is also accompanied by asymmetry--at least in so far as populations of relatively consanguineous individuals such as the Tristanites have on the average greater asymmetry than less inbred groups. Nevertheless, within this one population at least, the individual coefficient of consanguinity seems unrelated to the degree of asymmetry.

(b) Asymmetry likewise appears related to environmental stress in *Drosophila* and man. In the fruit fly fluctuating temperature has been specified as one such stress, but in

man environmental stress has only been defined in the most general of terms.

(c) Within an individual, level of asymmetry in unrelated traits will also be unrelated, and as Bader's work has shown this may even be true for characteristics within the same organ system such as the dentition. On the other hand the work of Sakai and Shimamoto and Adams and Niswander on teeth and dermatoglyphics suggest that among other things pleiotropy may manifest itself in terms of similar levels of asymmetry in two or more related systems.

In conclusion there appears to be ample evidence linking genetic and environmental stress to level of asymmetry. What remains unclear, especially in man, is the specific nature of the stresses that produce asymmetry. In view of the potential usefulness of asymmetry as a measure of the adaptedness of a population and as a tool for studying the relationships between otherwise seemingly unrelated traits, and in view of the promise that the literature holds in this respect, it makes sense to try to identify the specific kinds of stress that lead to asymmetry. Furthermore, the relative permanence of the teeth paleontologically, and the ease and reliability of measuring dental casts, makes the dentition the organ system of choice in the study of asymmetry in man.

Chapter 3

Factors Influencing the Dentition

It has long been assumed that the utility of the teeth for evolutionary or genetic studies rests on that part of their size and shape determined by heredity. It is generally further agreed that this hereditary part is the major determinant of size and shape, and that environmental factors can be ignored. Recent research on the quantitative inheritance of tooth size indicates that this assumption may be unwarranted. The aim of this chapter is to review this issue by (a) considering the evidence for an environmental component to human tooth size, and by (b) specifying the conditions under which the dentition proves most labile.

Studies on Human Tooth Size

The nature-nurture problem with respect to tooth size in man has been examined by both the Twin and Family Study methods. The procedures and limitations of each approach are generally well-known and will be considered briefly in context in the following discussions.

A. Twin Studies

Theoretically twins provide geneticists with a natural but limited experimental situation for analyzing the heritability of a trait. The intrapair variance between monozygotic twins is attributable to the environment since they share a common genetic make-up. In contrast, differences between dizygotic twins are both genetic and environmental because their genotypes are not identical. The ratio of dizygotic to monozygotic intrapair variances reflects these relationships. If most of the variability in a trait is produced by the environment this ratio will approach 1.0. On the other hand the greater the genetic component of variance the greater will be the upward divergence of the ratio from unity. The significance of this divergence can be statistically tested.

The work of Osborne et al. (1958) illustrates the method. A sample of 33 pairs of monozygotic and 21 pairs of like-sexed dizygotic twins was drawn from a population of New York City twins being studied at the Columbia Presbyterian Medical Center. All were Caucasians of predominantly NW European descent, and half were Jews and half non-Jews. Zygosity was tested by blood typing studies, and measurement of the six permanent anterior teeth of upper and lower jaws were taken from stone casts. The ratio of

the intrapair variances of MZ and DZ twins were statistically tested for each tooth and found significant at the 5% level. Genetic variance therefore accounted for a major portion of the total variance in size for the anterior permanent teeth.

There are three important limitations to this method. First is the assumption that on the average the environmental conditions are equivalent in the two types of twins, and comparable to the conditions affecting singletons. The validity of this viewpoint is questionable with respect to the maternal environment provided by the different chorio-placental relationships in twins, and between twins and singletons (Price, 1950). Secondly, it is impossible to determine how much of the similarity between monozygotic twins is due to a common environment and not identical genotype. The result is that the intrapair variance of identical twins does not necessarily estimate the exact environmental variance for the trait in singletons. Third, the test of the ratio of variances does not allow for an estimation of the relative contribution of genetic and environmental components. Thus the literature reveals a statistically significant genetic component of tooth size variance, but this does not exclude the possibility of biologically significant environmental effects. Neither does it prove it.

B. Family Studies

Family studies potentially provide a means for quantifying nature-nurture relationships in a way that twin studies can not. Most are based on the analysis of the correlations and covariances between siblings and between parents and their children. Three family studies of tooth size in man are discussed below.

In 1963 Hanna et al. studied the mesio-distal diameters of the dentition of 140 individuals from 36 families using the casts of the parents and all of their children in whom the permanent incisors were fully erupted. The sample included 36 sets of parents, 34 sons, and 34 daughters, each scored for dental size as deviations from the mid-parental mean of the family. The transformed scores were then subjected to a multivariate analysis. For all the incisors, sons had larger values than their fathers, and daughters had larger values than mothers. This represents a systematic age difference which the authors could not attribute to tooth wear and which may reflect a difference in nutritional status between the generations. Similarly the multivariate analysis of the distances within families "indicated that the heterogeneity observed in the raw data results from environmental rather than genetic differences within families. . ." (p. 1325).

Potter et al. (1968) analyzed the covariances in tooth size between relatives in families of Pima Indians. Pima living on reservations in southern Arizona were used to minimize environmental factors in the evaluation of autosomal or sex-linked additive and autosomal or sex-linked dominant genetic effects on the size of the permanent teeth. Dental casts of 635 individuals (309 males and 326 females) from 153 families were measured for mesio-distal and bucco-lingual diameters. A factor analysis of the raw data resolved the 56 tooth measurements taken to three common factors on the basis of which each individual was given three factor scores. These factor scores were then used in the study of the covariances between relatives.

Discrepancies were noted between the observed correlations and those expected on the basis of genetic relationships. This led the authors to speculate that

important environmental sources of variation exist which interact differentially with genotypes, particularly with those of different generations . . . generally higher correlations for sib-sib than for parent-offspring relationships . . . further reflect strong environmental effects on tooth size factors, since sibs are more likely to share a common environment than are parents and offspring (p. 97).

Finally Niswander and Chung (1965) in investigating the effect of inbreeding on tooth size in Japanese children

observed an increase of approximately 15-20 percent in the variance of tooth size with an increase in F from zero to 1/16. They argued that the added variance was not genetic in origin because the variance within sibs was the same in both inbred and outbred groups. In contrast, variability between inbred sibs was increased, suggesting that consanguineous children being more susceptible to the non-genetic aspects of their surroundings, more easily reflect the environmental differences between families.

To summarize at this point, heritability studies in man are disappointingly meager in what they reveal about the relative contribution of gene and environment to tooth size variance. Twin studies prove that genes are important, and family studies prove that the environment cannot be ignored. Unfortunately the relationships between heredity and environment are not accurately known because the human experimental situation is so limited. Animal research proves more flexible in this respect because it allows for close inbreeding and cross fostering strategies far beyond what is practicable in man. It also permits rigid control of the environment. To conclude this section we review one of the classic family studies in animals so that we may better estimate the quantitative parameters which elude us in our own species.

Heritability of Tooth Size in Mice

In 1965 Bader and Lehman investigated the hereditary and environmental components for three dental traits in the house mouse. The total hereditary variance or degree of genetic determination was estimated for the widths of the three lower molars with the results as indicated in Table 3.1a. A subsequent analysis by Bader (1965) determined the heritability or the proportion of the total phenotypic variance due to genes acting additively. On the basis of his mating scheme he was able to divide the phenotypic variance into additive genetic, maternal environmental, and other environmental variance components. The proportionate contributions of each source are given in Table 3.1b.

The evidence points to a strong genetic contribution to the determination of the first and second molars (66%) and somewhat less but substantial genetic determination of the third (47%). Environmental variance is also large and roughly half of it is due to non-genetic maternal factors. If this pattern proves to be general for mammals the following points may be made: (a) The maternal component of environmental influence on the teeth is the largest single source of environmental variation in the dentition; (b) the relationship between genetic and environmental components of tooth size varies from tooth to tooth; some

(a)			
	M_1	M_2	M_3
V_g	0.62	0.49	0.41

(b)			
	M_1	M_2	M_3
V_a	0.66	0.66	0.47
V_{ec}	0.18	0.17	0.26
V_{ew}	0.16	0.17	0.27

Table 3.1 (a) The degree of genetic determination (V_g) for the bucco-linqual diameters of the lower three molars of the common house mouse (*Mus musculus*).

(b) The percent contribution of the additive genetic variance (V_a), the variance common to litters (V_{ec}), and the variance of individuals within litters (V_{ew}). From Bader, 1965.

teeth will be more susceptible to environmental fluctuations than others; (c) environmental sources of tooth size variance are substantial enough to provide a range of variation sufficient to reveal linear relationships between environmental conditions and dimensional aspects of the teeth; and (d) later developing teeth (i.e. M_3) may be less canalized by the genes than are teeth which develop earlier in life (M_1 and M_2).

Of these points the first has become a focus of recent research on dental development. Unlike characteristics such as body weight, tooth size seems incapable of responding to post-weaning adjustments in the environment. Dental traits in the mouse, for example, are completely determined by the end of the nursing period so that according to Bader "the offspring has the effect of the maternal environment "frozen" for life" (1965: 383). In such cases the maternal environment becomes critical for understanding the development of the trait.

The importance of this research is that it underscores the inadequacies of the traditional view stated at the beginning of this chapter. The imperviousness of the teeth to postnatal environmental effects used to be taken as proof that the environment could be ignored in studying tooth size and shape. It now seems likely that this

represents an over generalization from the facts. Instead in man as in mice the effects of the maternal environment may be "frozen" early in life. The remainder of this chapter reviews the animal and human literature which supports this contention.

The Importance of the Maternal Environment in Tooth Development

A. Animal Studies

In 1951 Grueneberg noted that for mice

within each strain no matter what the mean size of its third molars, the size of these teeth varies with hitherto unidentified maternal conditions which tend to affect all the embryos of a litter alike (p. 449).

Mice from inbred mothers had smaller third molars than those from hybrids and Grueneberg suggested that improved physiology related to heterosis might explain this. Since that time there have been many studies aimed at assessing the significance of these 'hitherto unidentified maternal conditions' for the development of the teeth.

Kreshover (1953a; 1953b) in a series of investigations into the prenatal influences on tooth development, examined the effects of Alloxan Diabetes and induced fever in pregnant rats and the consequences for their litters.

In both studies delivered young were sacrificed at 1, 7, 21, 40, and 60 days of age. In the alloxanized group there were

no gross dental changes in the offspring but almost all of the experimental animals showed microscopic abnormalities of amelogenesis. In the induced fever experiment there were striking effects on amelogenesis ranging from ameloblastic dysfunction to complete cellular degeneration and arrest of enamel matrix formation.

Paynter and Grainger (1956) found that rats borne and nurtured by mothers whose diet was either abnormally high in phosphate content or deficient in vitamin A had smaller upper first molars than controls. Similarly, Holloway et al. (1961) observed that offspring of rats fed a low protein-high sucrose diet not only grew more slowly, but their molar teeth erupted later and were smaller in size than rats born to females fed a normal control diet. Even more important is that Holloway and coworkers reported that

. . . the change in size was due to a decrease in the distance between the outer borders of the dentine rather than to a reduction in enamel thickness. . . . these changes . . . must have been the result of a systemic influence operating early in tooth development, because the size and shape of the amelodentinal junction is determined before any calcification of enamel or dentine occurs (p. 197).

Shaw and Griffiths (1963) found that the offspring of rats on a low protein diet had higher mortality during lactation, low body weights at weaning, smaller molars, delayed eruption of the third molar, and increased

susceptibility to carious lesions. Searle (1954a; 1954b) has shown that first born litters of mice have congenitally missing third molars significantly more often than do later born litters, and that early litters from young mothers have the highest percentage of missing teeth. Also mice from pregnant mothers fed a low protein diet have smaller third molars than controls whose mothers are fed a normal diet.

It seems reasonable to conclude from such evidence that maternal factors determine a significant proportion of the dental variation in their offspring.

To further analyze the maternal influence on dental development it is possible to divide the maternal environment into a prenatal component reflecting intrauterine conditions, and a postnatal component affecting the young by altering the efficiency or quality of milk in the lactating mother. Although this distinction has not been observed in the cited literature, quantitative estimates of each component have been arrived at by Tenczar and Bader (1966). Having established that 16, 17 and 27 percent of the total variance of the first, second, and third molars respectively were attributable to maternal factors (Bader, 1966; see Table 3.1b), they attempted to delimit the relative contribution of each component by reciprocally cross-fostering 1/2

of each litter under study and observing the effects on molar size. The results showed that for the width of M_2 , between 21-29 percent of the total variance could be attributed to the prenatal environment, and only 7-11 percent to the weaning period. In contrast, M_3 which does not initiate differentiation until about 5 days after birth (as compared to the 16th day in utero for M_2) had no significant prenatal component to its variation. As per Holloway et al. (1961) the implication is that environmental influences are most critical during a limited period of dental development, when the ameloblasts and odontoblasts are in contact and determine the contour of the dentino-enamel junction. In the mouse this period coincides either with the end of gestation or the nursing period, depending on the tooth.

Finally, Riesenfeld (1970) in a study on the consequences of environmental stress on tooth development in the rat, observed that extreme inanition immediately after weaning and to six months of age decreases the crown dimensions of the lower first molar in the rat. It should be borne in mind, though, that this late postnatal lability is the result of grossly abnormal loss in body weight (up to 82.95 percent weight loss as compared to controls).

B. Human Studies

To my knowledge there is no direct evidence of maternal environmental influence on human tooth size per se, but several investigations have demonstrated an association between prenatal circumstances and tooth eruption.

Gyulavari (1961) found that children premature by birth weight (2500 gm or under) were retarded in tooth development at 9 and 10 years of age as compared to controls.

Bailit and Sung (1968) observed that the development of the mandibular permanent teeth in a sample of 289 children was significantly correlated with birth weight and maternal age, and Keene noted that children born prematurely by weight have more congenitally missing teeth (1968) and that the light born twin of monozygotic pairs has a tendency to be retarded in dental development (1966). Finally, Bailit et al. (1968) studied the relationship between several prenatal factors and tooth development in Japanese children. They found that tooth eruption was significantly retarded in low birth weight groups with a trend for tooth formation to be similarly retarded.

Summary

Several conclusions relevant to the hypothesis being tested in the present investigation can be drawn from the

evidence reviewed in this chapter: First, dental development with respect to size is detectably influenced by environmental factors; second, the teeth are susceptible to environmental influence during a limited period of their development, and there is some evidence that this period lies near or before the onset of dentinogenesis and amelogenesis; third, since in most mammals this critical period coincides with the late gestational and early postnatal period, non-genetic maternal factors are the most important source of environmental influence; and fourth, not all teeth are equally subject to maternal environmental factors because (a) some are more genetically determined than others, and (b) some develop prenatally and others postnatally and hence are differentially exposed to maternal influences.

Chapter 4

Birth Weight, Intrauterine Growth Rate, and Mortality and Morbidity in the Newborn

Chapter 3 has shown that the search for associations between dental asymmetry and stress must center on the perinatal stresses imposed by an inadequate maternal environment. This chapter searches for a basis of an operational definition of perinatal stress in man dependent on the relationship between maternal environmental factors and the health status of the neonate. In particular birth weight and fetal growth rate have become the most general indices of this health status because of their close association with mortality and morbidity in the newborn (for recent studies see: Akesson, 1966; Battaglia and Lubchenco, 1967; Brimblecomb et al., 1968; Casalaina et al., 1964; McEvan, 1966; Rantakallio, 1968, 1969; Schneider, 1969; Van den Berg, 1968; Van den Berg et al., 1968; and Yerushalmy, 1967). The issues involved are reviewed below.

Birth Weight and Survival

The most often quoted study showing the relationship

between birth weight and mortality is that of Karn and Penrose (1951). A significant difference between the mean birth weight of survivors and non-survivors was demonstrated for a sample of 13,730 British births. In particular this brought into focus the fact that low birth weight infants are at a greater risk of mortality at birth than other children, and that birth weight exhibits an intermediate optimum with respect to survival.

Several subsequent studies patterned on this model have produced similar results. Italian (Fraccaro, 1956), Indian (Jayant, 1964), Ghanaian (Hollingsworth, 1965), and English (Jayant, 1966) populations and diverse ethnic groups in Hawaii (Morton and Chung, 1967), though differing in overall mean birth weights and mortality rates, are consistent in having an intermediate optimal birth weight and in having significantly lighter birth weights in non-surviving children within their respective populations.

The Concept of Prematurity

Hollingsworth has noted that if birth weight were the major factor in neonatal and perinatal death, one would expect a consistent relationship between the overall mean birth weight and the mortality rates in different populations. This is not the case. Indian babies, for example,

though much lighter at birth than their English counterparts have slightly lower mean mortality rates. According to Hollingsworth "the factors involved in the relationship between birth weight and survival are complex and far from clear" (1965: 297).

It is now generally recognized that the complexity that Hollingsworth speaks of stems from the fact that birth weight is a major factor in perinatal risk both per se and as an index of maturity. The low birth weight child is in danger both because of his low birth weight and because his low birth weight reflects an overall level of immaturity. The historical development of this concept has been reviewed by Yerushalmy (1966) and Van den Berg and Yerushalmy (1966). An outline follows.

A. Prematurity and Gestational Age

The concept of prematurity is based on the notion that the birth in question occurs before the full or normal period of gestation has elapsed, with the presumptive consequence that the infant has been deprived of the full benefits of intrauterine life. That this assumption has some basis in fact is attested to by the demonstrable increase in mortality with shorter length of gestation. Steiner and Pomerance (1950) found that for 791 liveborn prematures

delivered at the Jewish Hospital of Brooklyn from 1941 to 1955, the fatality rate varied inversely with the length of gestation for any given birth weight range. Schlesinger and Alloway (1955) obtained similar results when studying 436,255 single livebirths over 20 weeks gestation delivered in New York State between 1940 and 1951. Decreasing mortalities with increasing gestational age are also reported by McKeown and Gibson (1951), Clifford et al. (1953), and Dunn (1965). However in these cases no attempts were made to control for concomitant variation in birth weight.

B. Prematurity and Birth Weight

Gestational age is not a usable clinical yardstick of prematurity because it is generally unreliable and not always knowable. Instead, since "mortality is so closely associated with both birth weight and duration of gestation that there is little to choose between them as indices of probability of survival" (McKeown and Gibson, 1951: the former has replaced gestational age as the standard of prematurity. Birth weight is easily and reliably measured and clinically useful for prognostication. Nonetheless, there has been a persistent awareness on the part of the researchers than this confusion of a physical measurement as a yardstick for a time period only obscures the issues involved.

C. Limitations of Birth Weight as a Measure of Prematurity

The limitation of birth weight as a criterion of neonatal maturity was recognized as early as Peckham's "Statistical Studies of Prematurity" in 1938. From a series of 4,055 births delivered at John's Hopkins Hospital, Peckham found that the mortality rate for the weight range 2,300 to 2,399 grams was 9.63 percent for whites and only 3.59 percent for blacks. Morton and Chung (1967) have shown similar discrepancies in mortality rates for given birth weight ranges in the various racial populations of Hawaii. The conclusion is that with respect to mortality risk a fixed birth weight value used as a standard of prematurity defines non-comparable population segments in interpopulation investigations.

Toback (1951) came to the same conclusion from the analysis of a more recent sample of Baltimore white and black newborns, but he also noted that the problem extends to intrapopulation studies as well. In a clinical sample of 656 white single births, he observed that 7.4 percent were mature with respect to birth weight (i.e., over 2500 gm) but less than 38 weeks in gestational age. Of those mature by gestational age, 3.3 percent were below 2500 gm in birth weight, and only 3.3 percent of the sample were immature in both birth weight and gestational age. Yerushalmy

et al. (1965) obtained similar results in studying over 400,000 New York City births between 1957 and 1959. Only 45 percent of births under 2500 gm were also under 37 weeks in gestation, and 20 percent of those under 2500 gm at birth were in utero 40 or more weeks. Evidently low birth weight children represent a very heterogeneous group, and this realization has led to a much needed restructuring of the prematurity concept.

D. The Modern Concept of Prematurity

The modern concept of prematurity has been extended beyond the intuitive notion of pre-term (see Yerushalmy et al., 1965). Instead the central idea now is that the pregnancy has terminated before the fetus has derived the full benefits of intrauterine life. This can mean either (1) that the fetus did not develop in utero long enough, or (2) that the fetus did not develop in utero well enough. Birth weight reflects both these possibilities but it can not distinguish between them. As a consequence, several alternative definitions of relative maturity have been proposed to replace the concept of prematurity by birth weight. (see Lubchenco, 1963; Gruenewald, 1961, 1963, 1964; Yerushalmy et al., 1965; and Van den Berg and Yerushalmy, 1966). All involve the idea of low birth weight

for gestational age, and can consequently be viewed as indices of intrauterine growth rate.

E. Intrauterine Growth Retardation

McBurney (1947) was one of the first to realize that low birth weight children with long gestational ages must be regarded as retarded in their intrauterine growth rate. Interest focuses on these children because of the relationship between intrauterine growth retardation (IUGR) and severe congenital anomalies. Warkany et al. (1961), for example, followed the case histories of several IUGR children with postnatal growth deficiencies. Although recognizing that theirs was a biased sample, they felt that the developmental disturbances which they studied were much more common in IUGR children than in full term children with birth weights within normal limits. Gruenwald (1963) likewise feels that chronic fetal distress resulting in IUGR is a "frequent antecedent and presumably a highly significant predisposing factor in morbidity and death" (ibid.: 224).

Evidence supporting this viewpoint is provided by Yerushalmy et al. (1965): Their group of children were divided into 5 categories by birth weight and gestational age. The most instructive differences were noted between

the category 1600-2500 gm and less than 37 weeks and the categories 1600-2500 gm and 37 weeks or more. The former had higher mortality rates than the latter, but the latter (growth rate retarded) had a higher incidence of congenital abnormalities.

Likewise Van den Berg and Yerushalmy (1966) divided a sample of low birth weight infants into 4 groups identical in their birth weight distribution and sex composition, but different in their length of gestation and hence in their IUG rate. Mortality to 2 years, frequency of congenital anomalies and morbidity were then compared in the four groups with the following results: (1) the shortest gestation group had the highest neonatal mortality rate with death generally associated with respiratory problems; but the longest gestation group (IUGR) had the highest mortality rate from congenital malformations; (2) The long term prognosis for mortality to 2 years indicated that the two extreme groups (shortest and longest gestation) were at greatest risk; and (3) In terms of morbidity, the IUGR group had the highest proportion of severe non-trivial congenital anomalies, and as a group (excluding those with severe congenital anomalies) were more often ill and lagging in physical growth to two years than the short gestation group.

Summary and Conclusion

Birth weight and gestational age, particularly considered concomitantly as a measure of maturity, are highly correlated with survival and morbidity in the newborn. As such birth weight and neonatal maturity are important indices of perinatal stress and may serve as the basis for an adequate operational definition of it. The usefulness of any such definition for the present study depend on the extent to which birth weight and neonatal maturity are functions of and limited by maternal factors. This is discussed in the next chapter.

Chapter 5

Factors Determining Birth Weight and Fetal Growth Rate

In the present study, perinatal stress is being defined in terms of birth weight and intrauterine growth rate. The justification for the use of this definition in terms of the general stresses affecting the neonate were presented in chapter 4. In chapter 3 we observed that the particular stresses of interest with respect to dental development are those which spring from inadequacies of the maternal environment. The assumption that we shall attempt to support in this chapter is that birth weight and fetal growth rate are largely determined by maternal factors and hence justifiably used as a measure of perinatal stress on the dentition. We shall then attempt to specify maternal conditions known to affect birth weight.

Environmental Sources of Birth Weight Variance

In broad outline the evidence to date suggests that birth weight variance in mammals is overwhelmingly environmental rather than genetic in origin. As early as 1938, with

Walton and Hammond's crosses of Shire and Shetland horses, it has been clear that the fetal genetic system is frequently suppressed in favor of maternal factors adapted to producing offspring commensurate with the mother's size. Newborn foals of Shire mares crossed to Shetland stallions are almost as large as pure Shire newborns, while offspring of the reciprocal cross are as small as newborn Shetlands. Cows (Joubert and Hammond, 1958), rabbits (Venge, 1950), sheep (Hunter, 1956), and mice (Brumby, 1960) respond similarly to such crossing experiments. In the latter three cases, the technique of egg transplantation, whereby eggs of a given genotype are transplanted into mothers of different sizes, demonstrates that the effects are mainly uterine and independent of the genetic constitution of the eggs. The size of the newborn covaries with the size of the mother when the genotype is held constant.

In man the intrauterine environment is apparently no less important than in other mammals. Robson, for example, found that the correlation in birth weight between cousins whose mothers were unrelated are much lower than the +0.125 expected for a completely additive autosomal genetic trait. On the other hand, cousins whose mothers were sisters exceeded that expectation. The implication is that the similarities between sisters extends to the constitutional

and physiological properties related to their child bearing capabilities. Children of such sisters are alike because of these similarities in their mothers.

Likewise, if birth weight were highly heritable, the intrapair variance of sibs from consanguineous matings should decrease because of their greater genetic similarity. In contrast, variance between such groups of sibs should increase. The available evidence (Morton, 1955) indicates that parental consanguinity has no apparent effect on the variance within and among pairs of full sibs from a sample of 63,000 Japanese children from Hiroshima and Nagasaki. In view of corroborating evidence from half-sibs and twins, Morton concludes that "all the available evidence is consistent with the hypothesis that the genotype of the fetus accounts for only a small part of the variance of human birth weight" (1955; 131).

Specific Maternal Factors Influencing Birth Weight

Many common maternal factors limiting birth weight and fetal growth rate have been studied to date. These include parity and maternal age; constitutional factors such as height, weight, and heart volume; hypertensive maternal disease; and maternal malnutrition. These are considered below.

A. Maternal Age and Parity

Karn and Penrose (1951) considered the effects of parity and maternal age on birth weight and survival in English children with results which were essentially duplicated by Fraccaro in Italian data. Both studies indicated that birth weight and parity were significantly and positively correlated variables even when the effects of maternal age are eliminated; on the other hand, the correlation between birth weight and maternal age is very small but positive when correction is made for parity. In contrast, Hollingsworth (1965) found that correlations between birth weight and both parity and maternal age were markedly reduced when corrections were made for the intercorrelation between the latter two variables. However, this sample also differed from the European data in having older mothers of higher parities among the non-surviving newborns. An Indian sample studied by Jayant (1964) conforms with the African pattern in having older mothers of higher parities among non-surviving newborns, but otherwise parallels the results obtained by Karn and Penrose, and Fraccaro. The latter also reports a significant correlation between birth weight and parity for a Czech sample of 167,731 births (1958). Unfortunately the data in this study did not allow a correction for the effects of maternal age so that the true contribution

of parity to birth weight could not be measured.

Some insight into the inconsistent behavior of maternal age reported above is provided in an investigation by Millis and Seng (1954) analyzing birth weight and maternal age within parity groups in a sample of 18,425 lower socioeconomic status Chinese infants born in Singapore in 1950-1951. Within each parity group the relationship between birth weight and maternal age was always linear, but slope and sign varied from parity to parity. If such inconsistent results obtain within a given sample, there is no reason to expect consistent generalizations between populations in this respect.

It is also difficult to make interpopulation generalizations with respect to parity effects. All of the European populations studied suggest that the rise in birth weight with parity falters and may decline in the higher parities. Thomson et al. (1968) observed that for a sample of 53,004 single legitimate births in Aberdeen during 1948-1964, parity had very little effect on birth weight after the first pregnancy. Clifford et al. (1953) noted that fetal and neonatal mortality rates increase from about 40 per 1000 to 90 per 1000 for women over 35 in their fourth or higher pregnancy. Given the relationship between low birth weight and mortality, this might indicate that the higher parities are

associated with lower birth weights.

Opposing this view, Pamilleri and Cremona (1970) argue that a curvilinear relationship between birth weight and parity may be restricted to Western industrialized populations where selection of mothers with higher parities is selection for lower socio-economic status. They claim that where large families are usual and not related to SES, a clear rise in birth weight with parity is evident. To support this claim they present evidence from a Maltese sample of 2,517 births showing a continual progression of birth weights with increasing parity. The sample is characterized by a wide range of parity and relative ethnic and social homogeneity.

Unfortunately the similarly controlled sample of Millis and Seng described above (p.) demonstrated a consistent and curvilinear pattern between birth weight and parity per age group of the mother for all age groups studied. The overall picture is thus confused, but one consistent feature that emerges for all populations is that first born children are lighter at birth than subsequent children irrespective of the mother's age.

B. Constitutional Factors

Among the constitutional factors known to be correlated

with birth weight of infants are the mother's height and weight. Lennér (1943) in one of the earliest studies of this kind noted a +0.19 correlation between mother's weight and that of the newborn. He also obtained a correlation of +0.18 with the father's weight, but Gawley et al. (1954) argue that the apparent effects of the father's height or weight can be discounted as spurious and are no doubt due to assortative mating patterns where large women tend to marry large men. When the maternal correlation between birth weight and stature is corrected for this association, it still remains positive and significant. The paternal value so corrected becomes insignificant.

McKeown and Record (1954) have confirmed this pattern in a series of 375 twin births. They further ascertained that the effect of maternal height on fetal size is not determined by an influence on the size of the placenta. Correlations between placental weight and maternal height are almost eliminated by correction for fetal weight.

Correlations between maternal weight, height or both on birth weight are also reported by Hytten et al. (1963), Love and Kinch (1965), O'Sullivan et al. (1965), Kauppinen (1967), Eastman et al. (1968), and Niswander et al. (1969). Such correlations probably account for the association between these constitutional factors and prematurity as

determined by birth weight. Thus Backman and Unnérus (1963) reported that for a sample of 704 deliveries in Helsinki, the mean weight of mothers of full term children was significantly greater than that of prematures. Height differences between the two groups of mothers did not differ. Likewise Scott and Usher (1966) noted that mothers of infants with fetal malnutrition weighed significantly less than control mothers, but that heights in the two groups were similar.

In contrast to this evidence Donnelly et al. (1964) observed that prematurity did correlate with maternal height in a series of 29,561 North Carolina live births between 1954 and 1961. Similarly a very large sample of single legitimate births in Aberdeen during 1948-1964 showed that for the shortest and lightest groups of mothers, 56 percent of their babies were below the 25th percentile of birth weight compared with 7 percent for the tallest and heaviest mothers (Thomson et al., 1968).

The disparities in these reports suggest that mothers' height and weight are complexly related to infants' birth weight. A considerable effort to resolve some of these complexities can be found in a large body of work by a Finnish group who have concluded that maternal heart volume is a primary determinant of infant birth weight (Raiha

et al.; Unnerus, 1959; Raiha and Kauppinen, 1963; Raiha, 1963, 1964; and Kauppinen, 1964). Their central argument as presented by Backman and Unnerus (1963) is that fetal development is dependent on the hemodynamic balance during pregnancy, where a circulatory capacity of small output (as monitored by heart volume) yields a uterine circulation more sensitive to an increased distribution of blood to other organs during work.

Backman and Unnerus (ibid.) found that mean placental weight and mean maternal heart volume were significantly different between two groups of mothers who had delivered term and premature babies (under 2500 gm at birth) respectively. In both cases the prematures had lower values, but whereas birth weight was correlated to both placental weight and maternal heart volume in full term infants, it was only correlated to placental weight in prematures. Placental size and circulation were overriding factors in prematures rather than maternal heart volume.

The significance of the association between maternal heart volume and birth weight has been questioned by several authors. Hedberg and Radberg (1962) working with 80 term and 80 prematures found that neither maternal weight nor heart volume were significantly correlated with birth weight when the data were corrected for length of gestation.

Furthermore, Hytten et al. (1963) have argued that one would expect small women in general to have proportionately small hearts and blood volume. Consequently the relationship between maternal heart volume and birth weight might be no more than another expression of the relationship between the size of the mother and birth weight. In 112 primagravids who delivered at term, heart volume was measured at 30 weeks gestation and a positive correlation was observed between the height of the woman and both heart volume and birth weight. The initial weak relationship between heart volume and birth weight disappeared, however, when the effect of height was taken into account.

In response to these criticisms, Kauppinen (1967) reexamined the relationship between birth weight and maternal absolute heart volume, maternal weight, maternal height, and maternal body surface. To clarify the relative contributions of these variables to birth weight, each was examined controlling for the others, and for maternal age, and parity. From 2268 primiparas 20 to 29 years of age, only mothers close to the mean value for height and weight were selected. This left 287 cases for whom the correlation between birth weight and maternal heart volume jumped from +0.19 to +0.63. When maternal heart volume was standardized on both sides of its mean, the correlation between birth weight and:

- (1) maternal weight decreased from $+0.17$ to $+0.08$.
- (2) maternal height decreased from $+0.18$ to $+0.10$, and
- (3) maternal body surface decreased from $+0.18$ to $+0.06$.

He concludes that contrary to Hytten et al. (1963) "the effect of the absolute heart volume . . . can be regarded as primary and that of weight and height as secondary" (p.

). Again as in the report of Backman and Unnérus (1963) this relationship did not obtain where the placenta was small (under 600 gm), and Kauppinen speculates that in such cases placental activity may be deficient and the relationship between heart volume and birth weight weakened for primary reasons.

One final topic of interest for this section is the study of the relevance of prepregnant weight, pregnancy weight gain, and the relationship between them as they affect birth weight outcome. In 1943, Kerr had shown that there was a tendency for increasing pregnancy weight gains to be associated with heavier infants, larger women tending to gain more weight during pregnancy than others. The correlation between weight gain and infant weight was ± 0.20 . Beilly and Kurland (1945) obtained a correlation of $+0.18$ for the same variables, but found that the average weight gain in light women was greater than that of the entire group as a whole, and that the average gain in the heavier women was

less than that of the entire group and the lighter women.

Recently there has been a reexamination of these factors and Singer et al. (1968) working with a sample of 10,000 children in the Collaborative Study of Cerebral Palsy have observed high weight gains related to higher birth weights and to decreased prematurity rates. They suggest that this relationship is independent of the mother's pre-pregnant weight since Stander and Pastore (1940) have shown that though birth weight is positively correlated to prepregnant weight, prepregnant weight is negatively correlated with weight gain. Eastman et al. (1968) argue that these two factors are not only independent of each other but that they operate additively. This notion is summarized in Figure 5.1 below.

	<u>Low wt. gain</u>	<u>High wt. gain</u>
Low prepreg. weight	- - -	- - -
High prepreg. weight	+ -	+ +

Figure 5.1 Illustration of Eastman's hypothesis of independent and additive contribution of prepregnant weight and weight gain during pregnancy, to birth weight (- - low birth weight; - + and + - intermediate birth weight; + + high birth weight).

Their test of this hypothesis was confirmed in a sample of 6675 full term white pregnancies and 5236 black births. It was independently corroborated by Niswander et al. (1969) in a similar study.

C. Hypertensive Disease and Maternal Malnutrition

McBurney (1947) was one of the first to associate maternal hypertensive disease with low birth weight in full term infants. He considered that such children were really undernourished as a consequence of impaired placental circulation and small placentae. Supporting evidence for this line of reasoning can be found in the work of Baird et al. (1957) who report that in a sample of 7,168 single births in Aberdeen (1948-1955), there was a tendency for unusually low birth weight in cases of severe pre-eclampsia where delivery took place before term. Similarly Fitzgerald and Clift (1958) found that in 819 cases of toxemia with 72 stillbirths or neonatal deaths, the Intrauterine Death by Toxemia Group suffered a stunting of fetal growth as compared to standards for fetal growth by gestational age.

The notion that such retardation of fetal growth comes about from the disturbance of placental circulation has been shown to be possible by several important studies.

Brown and Veall (1953) for example, compared the relative rates of maternal blood flow in the placentae of normal, pre-eclamptic, and chronic hypertensive women. In pre-eclampsia and chronic hypertension, blood flow between the 38th week and term was reduced to about 1/3 of that in normal women. Similarly Assali et al. (1954) showed that the uterine circulation participates in the overall vasoconstriction which is characteristic of toxemic pregnancies. In normal pregnancies the flow was 12 to 18cc/100 Gm of pregnant uterus / min. In the toxemic women, this was reduced to 8 to 12cc/100 Gm of pregnant uterus / min. Finally, testing for the clearance of radio-sodium from uterine muscle, Morris et al. (1955) found that the effective flow was about one-half the normal in mild cases of pre-eclampsia, and only one-fourth the normal in severe cases.

How this reduced blood flow effects fetal growth rate is suggested in a review article by Page (1969), According to this author, the evidence indicates that glucose supplies essentially all of the energy requirements of the fetus, and that the availability of glucose and insulin is the most important determinant of the growth rate of the human fetus. It is apparent from several studies involving the excision of the pituitary gland, that fetal growth

hormone is not responsible for fetal growth regulation. Instead fetal insulin appears to be the primary growth regulator. Insulin, however, acts only as a growth regulator in the presence of an adequate supply of glucose, and in as much as the maternal supply seems to be flow limited rather than diffusion limited, the final determinant of fetal growth may well be the rate of maternal blood flow across the total area of diffusing surface in the placenta. Page suggests, for example, that once a uterus has undergone pregnancy the vascular apparatus of the uterus is far more developed (see Baker, 1948) and parity effects between prima and multiparas might well be explained as a function of differential blood flow.

Younoszai et al. (1969) in studying placental weight, decidual surface area, mean thickness, and cord diameter in normal, pre-term, term, and IUGR infants, found that placental weight, decidual surface area, and cord diameter were significantly smaller in the IUGR infants as compared to those in the normal pre-term and term infants. Since birth weight was related to placental decidual area in all groups and to placental weight only in the normal pre-term and term infants, the suggestion is that placental decidual area may be an important determinant of infant birth weight. This is certainly in accord with Page's

suggestions that the final determinant of fetal growth may be the rate of maternal blood flow across the total area of diffusing surface in the placenta.

If as Page suggests the supply of glucose to the fetus is essential to its growth regulation, it is possible that the several reported instances of low birth weight with maternal malnutrition are a related phenomenon. The classic study of this is Smith's (1947) report on the effect of maternal undernutrition upon the newborn infant in Holland during the seige of 1944-1945. During this time a generalized malnutrition severely limiting intakes of total energy resulted in markedly decreased birth weights. It rose after the restoration of food, indicating that fetal weight gain is particularly related to maternal diet in the last half of the last trimester. Prematurity was of course significantly increased by this undernutrition. Stillbirth, neonatal mortality rates, and congenital malformations, however, did not increase. Similarly, Gruenwald et al. (1967) studying changes in Japanese birth weight over a 20 year period during which there was a recovery from war time deprivation, and increased mean birth weight over pre-war levels, found that fetal growth curves showed a striking increase of weight for gestational age for the later part of the third trimester as socio-economic conditions improved.

Other evidence of the importance of socio-economic factors on reproductive performance has recently been reported by Naeye et al. (1969). From 252 cases of perinatal mortality at the Babies' Hospital in New York City classified as poor or non-poor on the basis of weekly income and family size, 37 percent of all the poor mortalities were stillbirths compared to only 27 percent of the non-poor deaths. Undernutrition appeared to be responsible for the prenatal growth retardation in infants from poor families, since both mass of adipose tissue and size of individual fat cells were smaller in the infants from poverty families. The thymus, spleen, liver, and adrenal glands were relatively smaller than brain, kidney, heart, and skeletal bone as is commonly observed in chronic alimentary undernutrition.

Hendricks (1967) comparing the relative contribution of ethnic versus socio-economic status factors on reproductive performance, found that the affluent groups regardless of ethnic affiliation were superior in terms of perinatal mortality, incidence of prematurity by weight, prematurity by weeks, ectopic pregnancy, and pre-eclampsia. To this may be added the studies of Scott et al. (1950) and Knobloch and Pasamanick (1960), all of which point to the conclusion that maternal nutrition as reflected in socio-

economic status can have an important bearing on birth weight and fetal growth rate.

Summary and Conclusions

The evidence reviewed above indicates that in so far as there is variation in our sample for the maternal factors discussed in this chapter, birth weight and fetal growth rate can not be used as the measure of perinatal stress without controlling for differences in parity, maternal age, mother's size, and socio-economic factors. Within the limits permitted by the availability of data such considerations have been incorporated into the statistical methodology described in chapter 7.

Chapter 6

Evidence for the Lasting Postnatal Effects of Prenatal Deprivation

One remaining issue to be discussed in our hypothesis is whether or not children who are stressed perinatally manifest this in later life and are in part poorer health risks as a consequence. Below we review some of the pertinent literature that corroborate the existence of lasting postnatal effects of the prenatal environment on non-dental traits.

Animal Studies

The importance of nutritional factors during the perinatal period on the subsequent development of the mammalian organism is well illustrated in two controlled studies with mice and rats. Widdowson and McCance (1963) examined the effects of finite periods of undernutrition at different ages in the body composition and subsequent development of the rat. They found that a setback after weaning was much less serious than one before it. The older an animal grows and the slower its growth rate, the less

irreparable the damage done by undernutrition. However, even when a deprived animal had recouped body weight by rapid growth following undernutrition, it did not result in an animal identical in body composition with one that had reached the same weight by slow steady growth. In particular they noted that organs with a strongly anabolic metabolism such as the stomach, or continuous activity, such as bones, continue to grow at the expense of others which were drawn upon for amino acids or calories. It would be interesting to know what the effects of such differences in body composition are with respect to longevity, but this evidence is not presented.

In mice, it has been shown (Dubos et al. 1968) that the diet of the mother during gestation and lactation, or during lactation alone, effected the weight of their pups at weaning time and throughout their whole life span. Minor alterations of the dam's diet (deprivation of threonine or lysine) produced a lasting growth depressing effect throughout life even though they were given an optimum diet in unlimited supply at weaning and thereafter. The weight depressing effect of a threonine and lysine deficient diet administered to adult mice, in contrast, was completely reversible upon restoration of the complete diet. No adverse effects on health and longevity were observed in the mice deprived nutritionally in the perinatal period.

Human Studies

A summary of the literature up to 1953 (Alin, 1953) reveals at least the following points of agreement between studies on human prematurity up to that time: (1) Physical and mental development of prematures lags behind that of maturely born children during the first two to three years of life. The degree of retardation seems to be inversely proportional to birth weight; and (2) nervous disorders are more common in prematures than matures. The symptoms displayed include increased fatigability, disturbances of sleep, anxiety, shyness, irritability, emotional outbursts, short attention span, poor memory, and lack of concentration.

To follow up on these reports, Alin studied a sample of 999 boys with birth weights below 2500 gm born in Stockholm between 1902 and 1921, and compared them to 1002 maturely born controls. He found that postnatal mortality was higher for prematures, especially during the first months of life. The rates do not even out between the two groups until two and three years of age, and most of the differential in mortality was associated with excess deaths from infectious diseases among prematures. With respect to physical development at adulthood, he found that prematures were significantly shorter in stature and lighter in weight.

Mean height at 20 years was 172.8 cm for prematures as opposed to 175.6 cm in full term births, and weight 64.0 kg versus 67.0 kg in the two groups respectively.

In 1965 Harper and Weiner reviewed three major longitudinal studies on the sequelae of low birth weight. These included: (1) a series of studies by Drillien including 251 surviving low birth weight singletons born in Edinburgh between 1953-1955, and 119 mature controls. (2) The Baltimore study, including 500 surviving prematures born in Baltimore in 1952 compared to 500 mature controls matched for maternal age, race, parity, and socio-economic status; and (3) A study by Douglas, et al. of 700 LBW children born in Great Britain during March of 1946, and a control group matched for sex, parity, maternal age, and social class.

The general findings with respect to physical growth show that LBW children continue to be smaller in height and weight than mature controls for the first decade of life. Drillien (1961) found prematures shorter and lighter at every age through 5 years. Of particular interest is the fact that children born 4-1/2 - 5-1/2 lbs at or near term were both shorter and lighter at 4 years than children of like birth weight who were premature by gestational age as well as by weight. This suggests that intrauterine growth retardation has to be distinguished from pre-term light

birth weight, and that the long term prognosis for the two might be different.

The Douglas study (1953) found that at 4 years of age 2/3 of the LBW children weighed less than the controls, and 44 percent were shorter. Likewise, the Baltimore study found LBW children to average 5-7 percent lighter and 2 percent shorter at all examinations through nine years of age.

With respect to morbidity, premature infants suffer from more medical illnesses in the first year of life than controls, especially from respiratory infections. The incidence of major and minor defects also increases with decreasing birth weight (Drillien, 1959). The Baltimore study found significantly greater frequencies of hospitalizations in the premature groups for children between 3-5 and 6-7 years of age. Drillien also reports that hospital admissions for medical illness were considerably higher for the prematurely born, again, especially for lower respiratory infections.

Lower intelligence test scores are also reported for LBW children. Drillien noted progressively lower intelligence scores with increasing low birth weight, and in a more recent study of children born weighing less than three lbs. found that 61 percent scored below 90 in IQ (Drillien, 1967). However, in research where grossly

impaired children are specifically excluded, there are small IQ differences, indicating that most children of LBW fall within normal IQ ranges. It would be important to know how full-term LBW children compare to pre-term LBW groups in this respect. Grossly impaired children would most likely come from the intrauterine growth retarded group, although this point has not been investigated.

Wohlmuth et al. (1965) considered the late effects of premature birth in 193 children of school age and found most of these children to be of low stature and slender. They included 6 cases of grave nervous disturbances, 91 cases of slight psychomotor retardation, hearing defects in 6, and behavioral disorders in 114.

Heimer and Freedman (1965) took several measurements of weight and height, head circumference, and occipitofrontal and biparietal diameters during the first 2-1/2 years of life on 311 singleton Black infants up to 2100 gm at birth. These were then compared to a standard of 50 full-term singleton births of similar socio-economic status. Among the prematures 19 percent showed some evidence of neurological impairment at 2-1/2 years. Growth attainment at 2-1/2 years for prematures of the same birth weight was greater among those of low gestational age--again, pointing to a difference between intrauterine growth retarded and other low birth

weight children. Also of considerable interest to the present study is the finding that children with neurological impairment had smaller measurements at 2-1/2 years than either unimpaired prematures or the term child.

Wilson et al. (1967) compared children with fetal growth retardation to children of normal weight for gestational age with respect to fibular growth and development of the epiphyses. They found that the growth retarded infants had smaller fibulae and retarded epiphyseal development, but that the neonatal growth rate of the two groups was similar. Of the 30 infants with fetal growth retardation, three showed severe retardation of neonatal fibular growth and severe physiological disturbances in postnatal life resulting from congenital anomalies. It would appear, therefore, that approximately 10 percent of intra-uterine growth retarded (IUGR) infants have significant congenital malformations that interfere with postnatal growth, but that the majority of such IUGR children grow at an adequate normal rate postnatally. The authors conclude that

it seems likely that fetal growth retardation, like prematurity, has many causes. If these causes are genetically or developmentally intrinsic to the infant, growth after birth may continue to be unsatisfactory. On the other hand, if the causes for growth failure are due to fetal-maternal relationships but extrinsic

to the infant, postnatal growth may proceed in normal manner (p. 222).

Finally, Sinclair et al. (1969), studying the difference in postnatal growth between LBW infants of different gestational age quartiles, found that the IUGR infants (long gestation quartile) grew rapidly at first, but then fell behind those with a fast intrauterine growth rate. They conclude that

it is clear that in any consideration of the sequelae of low birth weight, the contribution of fetal growth retardation to the low birth weight sample should be distinguished, and individual consideration given to the 2 groups: those whose low birth weight is due primarily to short gestation and those in whom it is due primarily to retarded rate of fetal growth. . . . (p. 316).

Summary and Conclusions

To summarize the important points relating to the present study: (1) it seems clear that factors determining low birth weight have a lasting retarding effect on the postnatal physical development of the individual at least through the first decade of life, and possibly through adulthood. This is probably especially true for LBW children born at or near term--that is, IUGR infants. (2) These same children are more susceptible to mortality and morbidity at least through the early years of life (i.e. birth to four years), and (3) their retarded rates of growth are associated

with retarded mental development, although this may be restricted to those cases of severe retardation associated with severe congenital anomalies.

Chapter 7

Methodological Considerations

This chapter considers the methodological strategies that underlie the analysis and interpretation of the data collected for this study. These strategies include sampling history, method and problems, data collection, measurement definition, validity and reliability, the variables included, and the statistical methodology.

Data Collection

Data collection for the variables included in this study occurred at three different times with different research objectives behind each collection. The method and reasons for each sampling are described below.

A. Data Collected between 1948-1953

The sample for the present study is a subset of a larger body of data collected under the auspices of the Atomic Bomb Casualty Committee (henceforth ABCC), and thoroughly described by Neel and Schull (1956) and Schull and Neel (1965). Most of the material was originally gathered in an

attempt to ascertain the genetic effects of the atomic bombs. The data were from children born to exposed survivors of Hiroshima and Nagasaki and were collected under the continuation of a voluntary wartime pregnancy registration program designed to ensure pregnant women access to necessary commodities in scarce supply.

To take advantage of this registration procedure, the ABCC distributed a questionnaire evaluating the effects of bomb exposure on pregnancy termination. At the time of registration for rationing, on or about the fifth lunar month of pregnancy, the first part of the questionnaire was administered by a special clerk. The woman's attendant completed the remainder of the form at delivery, and shortly thereafter a physician connected with the project examined the child.

B. Data Collected Between 1958-1960

In view of the relatively high incidence of consanguineous marriage in Japan, and in view of the availability of consanguinity data in the original study, a follow-up program was initiated in September of 1958 and continued until August of 1960. The objectives of this program were to assess the effects of inbreeding on mortality and morbidity in the offspring of consanguineous matings. From the 76,626 pregnancy terminations evaluated in the earlier radiation study a large sample of inbred and non-inbred children was selected.

These children were from parents who had not been exposed to radiation and for whom all the relevant prenatal parameters were known. The children were then examined for: a) a standard pediatric evaluation; b) neurological and psychometric tests; c) X-rays; d) laboratory examinations for blood, urine, and stool, and a serological test for syphilis; e) a series of ten anthropometric measurements; and f) a dental examination, including dental casts in the Hiroshima data.

Some of the results of this work are presented in the now classic The Effects of Inbreeding in Japanese Children. (Schull and Neel, 1965) and in a series of smaller papers that have appeared from time to time (Morton, 1958; Neel and Schull, 1962; Schull, 1958a, 1962; Schull and Neel, 1959, 1962). Also utilizing this material is the study of inbreeding effects on dental size in Japanese children by Niswander and Chung (1965) mentioned in Chapter 2.

C. Data Collection for This Study

In the summer of 1970 the IBM coded data cards for the various parameters of the children from this inbreeding study together with the unmeasured dental casts of the Hiroshima group were made available to me through the courtesy of Dr. Howard Bailit of the School of Dental Medicine, University of Connecticut. In all, 2666 individual records were included in the card file. Presumably a corresponding number of pairs

of dental casts could be matched to the individual cards by a common identification number; in fact, from the 518 sets of casts chosen for measurement, it was possible to match 501 to the appropriate card data. A sample size of roughly 500 is very large as regards the statistics of correlation and we therefore concluded data collection at this point.

Comparability of Samples

The aim in choosing this subset of 518 was to sample representatively from the larger group with respect to the prenatal parameters and with respect to the distribution of asymmetry. That the former objective has been achieved by the selection process is clearly demonstrated by a consideration of the descriptive statistics between the dental group and the remaining 'non-dental' sample (see Table 7.1). Between the two groups, for example, average maternal age for the sexes combined is identical. Very nearly identical values are obtained between the groups for mean number of conceptions, mean gestational age, and mean birth weight. On the other hand, differences between the sexes within either group although generally small are by and large greater than differences between the two groups. In short, with respect to the prenatal parameters, the subsample seems representative of the larger group from which it is drawn.

		(a)			
		<u>Dental</u>		<u>Non-Dental</u>	
Maternal Age	$\bar{X}$	27.29		27.29	
	S.D.	4.94		4.79	
No. of Conceptions	$\bar{X}$	2.78		2.70	
	S.D.	1.72		1.65	
Gestational Age	$\bar{X}$	40.13		40.14	
	S.D.	2.17		2.08	
Birth Weight	$\bar{X}$	303.31		306.98	
	S.D.	39.70		41.42	

		(b)			
		<u>Dental</u> Males/Females		<u>Non-Dental</u> Males/Females	
Maternal Age	$\bar{X}$	27.13	27.44	27.30	27.20
	S.D.	4.66	4.84	5.21	4.75
No. of Conceptions	$\bar{X}$	2.66	2.83	2.69	2.71
	S.D.	1.68	1.75	1.67	1.62
Gestational Age	$\bar{X}$	40.02	40.24	40.06	40.23
	S.D.	2.13	2.21	2.12	2.03
Birth Weight	$\bar{X}$	304.86	301.79	311.13	302.52
	S.D.	40.32	39.12	41.29	41.19

Table 7.1 A comparison of the descriptive statistics between the Dental (N = 493) and the Non-Dental (N = 2100) samples for maternal age, number of conceptions, gestational age, and birth weight:
 (a) sexes combined.
 (b) sexes considered separately.

Selection of Casts

The selection procedure consisted of arbitrarily picking sets of casts and including them in the study if they were measurable on both sides with respect to the upper and lower lateral incisors and first molars. Measurability reduced to a function of the quality of the cast, the number of teeth erupted on both sides, and the extent and position of dental caries. The procedure was subjective in the sense that no specific number of measurable teeth was ever established as a minimum criterion for inclusion. In general, acceptable children showed at least two sets of measurable antimeres, and consequently few individuals are represented by less than two sets of measurements.

Casts were not rejected because of malocclusion in contrast to the Niswander and Chung study (1965). Thus if prenatal stress and asymmetry is associated with malocclusion no bias is introduced on this account by the selection procedure. On the other hand if stress or developmental 'noise' is associated with asymmetrical delay of eruption, and with the position and extent of dental caries, the sampling procedure would exclude such individuals. Since right and left teeth must be present and measurable to study asymmetry in size, this remains a potential source of bias.

The Measurements

The measurements chosen for study were the standard mesio-distal diameters of the upper and lower lateral permanent incisors measured as the maximum diameter parallel to the occlusal plane; the mesio-distal diameter of the upper and lower first permanent molars also measured as the maximum distance parallel to the occlusal plane; and a modified bucco-lingual diameter of the first molars specially defined as follows.

A. For the upper molar:

Two imaginary lines between the paracone and the metacone, and between the protocone and the hypocone were bisected and the distance between the two points of bisection measured as the bucco-lingual diameter.

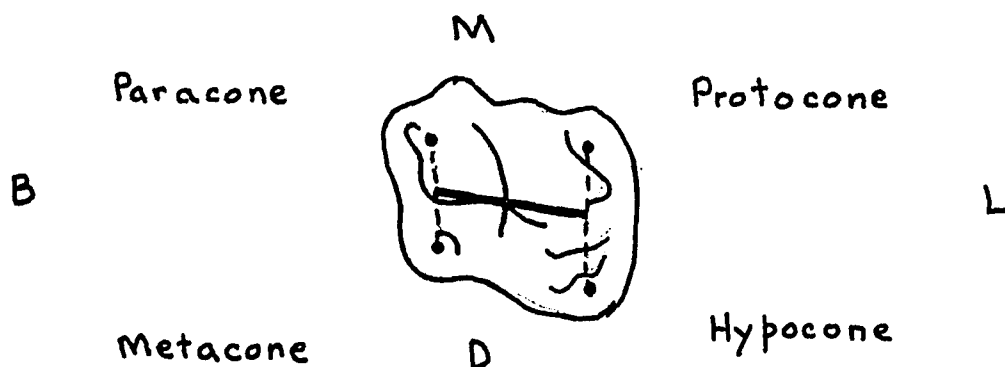


Figure 7.1. Drawing showing the bucco-lingual distance measured as the bucco-lingual diameter for the upper first permanent molar (dark line).

B. For the lower molar:

Two imaginary lines between the entoconid and the

metaconid, and between the protoconid and the hypoconid, were bisected and the distance between the two points of bisection used as the measurement.

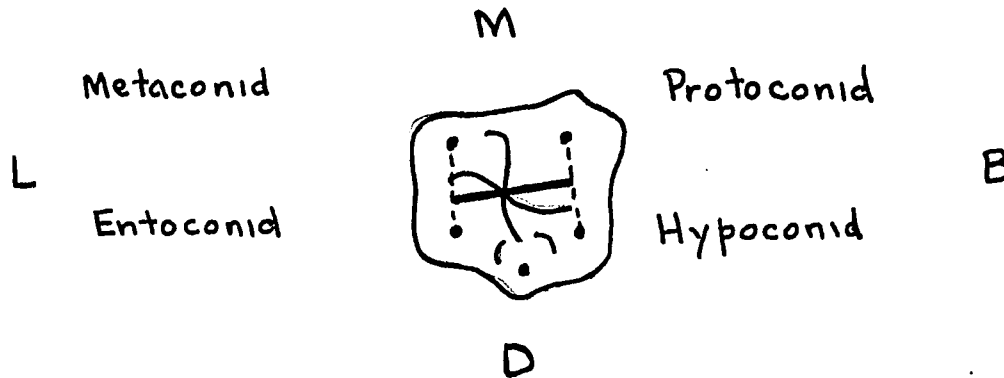


Figure 7.2. Drawing showing the bucco-lingual diameter measured for the lower first permanent molar (dark line).

This non-standard definition of the bucco-lingual diameter was chosen because the standard definition did not meet the requirements of reliability as discussed below (p.

In contrast the new measurement proposed, though limited by cusp wear or faulty cusp representation in the cast, remained a useful measurement and is retained in the analysis.

Choice of Teeth

The choice of the lateral incisors and the first molars reflects a multiplicity of reasons foremost among which are the following: (a) these teeth were most often erupted bilaterally in the children of the age group studied (6-12); (b) the upper lateral incisor represents the unstable tooth

in its morphological class and thus can be considered a likely respondent to stress. In contrast, the lower lateral incisor is the stable 'key' tooth (Dahlberg, 1945) and should provide interesting comparisons to its maxillary counterpart; and (c) the incisors as compared to the first molars undergo calcification postnatally, whereas the first molar begins to calcify prenatally (Massler and Schour, 1940). Although the evidence in Chapter 6 leads us to believe that prenatal factors are paramount in the determination of size, a contrast in the susceptibility of the two teeth to asymmetry and stress pre and post natally must be considered as potentially possible.

The Reliability of the Measurements

In view of the fact that asymmetry between antimeres is generally a very small quantity (i.e. measured as the absolute difference between right and left sides), it is necessary to make some observations as to the reliability of asymmetry measurements. If measurement error can be as large as left-right differences between the teeth, the attempt to measure asymmetry would be hopelessly confounded with such error. Fortunately some quantitative assessment of the relationship between measurement error and asymmetry is possible.

For a small set of casts repeat measurements were taken

after a long enough interval to prevent bias on the part of the measurer. Thus for any tooth in this set there are two measurements, the difference between which is a function of measurement error. The variance of this error can be expressed as the intrapair variance between first and second measurements:

$$\text{Error Variance} = \frac{\sum (x_1 - x_2)^2}{2N}, \quad df = N.$$

Since right and left antimeres are ideally symmetrical they may be pooled as representatives of the class rather than treated as separate entities. Symbolically

$$\text{Error Variance} = \left(\frac{\sum (L_1 - L_2)^2}{2N_L} + \frac{\sum (R_1 - R_2)^2}{2N_R} \right),$$

$$df = N_L + N_R,$$

where N stands for the number of pairs, L stands for left and R for right, and the numerical subscripts stand for first and second measurements.

Asymmetry variance can also be expressed as an intrapair variance. In this case it is a difference between left and right rather than first and second measurements, and since antimeres were measured twice, there are two estimates of asymmetry for any given pair. These may be pooled:

Thus

$$\text{Asymmetry Variance} = \left(\frac{\sum (L_1 - R_1)^2}{2N_1} + \frac{\sum (L_2 - R_2)^2}{2N_2} \right),$$

$$df = N_1 + N_2,$$

where N stands for the number of pairs, L and R for left and

right, and the numerical subscripts for first and second measurement.

The important question in terms of measurement reliability is if the variation due to asymmetry exceeds the variation due to error--i.e. do the differences between right and left teeth exceed the difference between first and second measurements of a tooth? This can be determined by considering the significance of the ratio of Asymmetry Variance to Error Variance:

$$F = \text{Asymmetry Variance} / \text{Error Variance}.$$

Such an analysis has been carried out for the six measurements used in the present study and the results are presented in Table 7.2. In all cases the symmetry variance exceeds the error variance and these differences are significant in all but one case at the 0.05 level. For the buccolingual diameter of the upper first molar the F value is very nearly significant and since the sample size involving its use is very large (369 cases) it is retained in the analysis. In short there is every reason to believe that asymmetry is practically measurable in terms of reliability, and asymmetry was thus simply defined as the absolute difference between the Napierian log transform of the left and right measurements multiplied by a scaling constant to facilitate the computational procedure:

Tooth	Diameter	Asymmetry Var.	Error Var,	F	df
Upper Lat. Incisor	MD	13.7	3.6	3.82*	41,41
Lower Lat. Incisor	MD	4.0	2.1	1.88*	47,47
Upper First Molar	MD	34.2	14.0	2.44*	24,24
	BL	12.7	8.9	1.43	40,40
Lower First Molar	MD	27.8	5.9	4.70*	28,28
	BL	20.2	10.8	1.88*	34,34

Table 7.2 Reliability estimates of asymmetry measurements for six diameters of the permanent teeth. Significance at the 0.05 level is indicated by an asterisk, and MD and BL stand for mesio-distal and bucco-lingual respectively.

$$\text{Asy.} = \text{ABS} ((\text{Alog L}) - (\text{Alog R})) \times 10,000.$$

The log transform was used to correct for the greater significance attached to a given difference between right and left in a small tooth as compared to a larger one.

Variables Included in the Study

Table 7.3 lists all of the variables utilized in this study. The dental variables include size and asymmetry measures obtained by the author, as well as the number of primary and permanent teeth, and measures of dental health (SMF and DEF). The pre- and postnatal parameters used were chosen for their relevance to the issues and problems discussed in chapters 4, 5, and 6. Due to limitations in the availability of data, it was not possible to include all the potentially significant parameters that affect our hypothesis as discussed in these chapters. The available data, however, adequately surveys what we feel to be the most significant of these factors. These are discussed below.

Birth weight and fetal growth rate are the key measures of prenatal stress as defined in chapter 4. Birth weight and gestational age are known for our sample, and together they give us an adequate measure of fetal growth rate. Of the concomitant maternal factors which might affect both birth weight and fetal growth rate, parity, maternal age, and

Table 7.3 List of the variables included in this study.

- 1- Maternal age (Mat.Age)
- 2- Number of Conceptions (No.Concp)
- 3- Coefficient of Consanguinity (Consang.)
- 4- Gestational Age (Gest.Age)
- 5- Sex
- 6- Number of Mats Per Person (Mats.Per)
- 7- Food Costs Per Person (Food.Per)
- 8- Number of Stillbirths in Mother's History (No.Stlb)
- 9- Birth Weight (Birth.Wt)
- 10- Asymmetry of I^2MD^* (Dents01)
- 11- Size of I^2MD (Dents02)
- 12- Asymmetry of I_2MD (Dents03)
- 13- Size of I_2MD (Dents04)
- 14- Asymmetry of M^1MD (Dents05)
- 15- Size of M^1MD (Dents06)
- 16- Asymmetry of M_1MD (Dents 07)
- 17- Size of M_1MD (Dents08)
- 18- Asymmetry of M^1BL^{**} (Dents09)
- 19- Size of M^1BL (Dents10)
- 20- Asymmetry of M_1BL (Dents11)
- 21- Size of M_1BL (Dents12)
- 22- Age of Child (Age)
- 23- Number of Permanent Teeth Erupted (No.Per.T)

- 24- Number of Decayed, Missing or Filled Permanent Teeth (DMF)
- 25- Number of Confinements in Bed for Two Weeks or More Due to Illness (Bed.2.Wk)
- 26- Number of Febrile Convulsive Attacks (Convuls)
- 27- Number of Primary Teeth (No.Pri.T)
- 28- Number of Decayed, Extracted and Filled Primary Teeth (DEF)

*MD indicates the mesiodistal diameter.

**BL indicates the buccolingual diameter.

number of previous stillbirths in the mother's history are known and can be controlled for by the proper statistical methodology. The possibility that the fetal genotype itself might limit birth weight is also controlled for by inclusion of the individual coefficients of consanguinity for the children.

Unfortunately various aspects of the maternal constitution such as height, prepregnant weight, pregnancy weight gain, and maternal heart volume, as well as evidence of maternal hypertensive disease, are not known for this sample. The uncontrolled effects of these variables on birth weight presumably increases the unexplained variance in birth weight and hence weakens any correlation between birth weight and asymmetry. To some extent the relatively small order of the correlations between birth weight and these variables recorded in the literature (see chapter 5) mitigates against the seriousness of this limitation.

Assessment of the postnatal environment for this study has been made by two measures of socio-economic status. The number of mats per person gives a measure of the density of the household and hence of the distribution of limited resources to its members; food costs per person give a rough measure of the relative nutritional status of the child's home. Although these measures reflect the SES of the parents

when the child was from 6-12 years old, Bailit et al. (1968), in a study using comparable data on children from Nagasaki, consider it probable that the same conditions prevailed at the time of the child's birth. This view is not consistent with the secular trend toward increasing birth weight concomitant with the economic recovery of postwar Japan reported by Gruenwald et al. (1967). For this reason we do not take the available measures of SES as a direct indication of the degree of environmental stress on the mother at the time of pregnancy. SES as measured in this study can not be reliably used as an indication of the kind of malnutrition known to affect birth weight in other wartime populations, however indirect evidence of such effects are reported in chapter 9.

As a final point we may consider the measures of postnatal morbid risks available for this sample. The number of times a child was sick in bed for two weeks or hospitalized, and the number of convulsive attacks suffered by a child, are direct but rough indicators of the child's postnatal health status. These are the only direct measures available and clearly leave much to be desired since they only assess the frequency of serious illness but do not specify the nature of the disease or its significance to the viability of the child. They should nonetheless serve as a useful first approximation to the problem.

Empirical Expectations

Given our review of the literature in the previous chapters, we would expect the following associations to emerge if our hypothesis is true:

1) Higher asymmetry in general would be associated with low birth weight and higher gestational age;

a - such asymmetrical children would probably have young mothers for whom they are the first child;

b- if such low birth weight/high gestational age children represent higher parities for their mothers, we would expect these mothers to have a history including previous stillborn children.

2) The above relationships might be most manifest in the asymmetry of the upper and lower first permanent molars, demonstrating a critical period of prenatal development for these teeth.

3) Higher asymmetry in general would be associated with poor socio-economic status. This would involve

a - fewer mats per person, and

b - lower food costs per person.

4) Asymmetry in '3' above might be most manifested in the upper lateral incisors, and be independent of prenatal factors.

5) Higher asymmetry in general would be associated with higher degrees of consanguinity.

Assuming that the above relationships hold:

6) High asymmetry would be associated with high post-natal morbid risk, including:

- a - a higher incidence of febrile convulsions,
- b - a higher incidence of confinement in bed for two or more weeks, due to illness,
- c - retarded dental growth as manifested in delayed eruption of the permanent teeth, and
- d - perhaps poorer dental health as manifested in high numbers of decayed, extracted, filled, or missing teeth.

Since the size of the teeth might be influenced by the same factors that affect asymmetry, we might find that:

7) High asymmetry is associated with smaller teeth, either

- a - representing an indirect relationship based on their common association with poor prenatal environment, or
- b - based on their common association with some intrinsic limitation of the fetal genotype not dependent on the maternal environment.
- c - If the latter proves true, we might reasonably

expect higher degrees of consanguinity to underlie such intrinsic limitations of the fetal genotype.

Statistical Methodology

A. Aim

The aim of our analysis is to explore the relationship within the individual between various pre- and postnatal parameters (the predictor domain) and dental asymmetry (the criterion domain). Interrelationships are generally measured by correlational techniques, but simple bivariate or multiple correlation models are inadequate with our data because each individual has several measures of dental asymmetry to be correlated with a fixed set of pre- or postnatal variables. Obviously the bivariate correlations between all possible pairs that could be drawn between the two domains would yield too many correlations to think about simultaneously. It would be very difficult to try to generalize about the extent and nature of interrelationships between the two domains on this basis. Furthermore, if we were to correlate each asymmetry value separately against the predictor domain (as in multiple correlation) the proliferation of tests is considerable. Again it would be very difficult to interpret the many test results because the likelihood of Type I errors increases with the number of tests.

Fortunately a multivariate technique developed by Hotelling (1935, 1936) enables us to express the degree of relationship between two sets of measurements made on the same subject. This method, canonical correlation, allows us to correlate the asymmetry domain as a whole against the predictor domain, and will specify which if any of the individual asymmetry measures most contributes to this correlation.

B. Method (Paraphrased from Cooley-Lohnes, 1971)

Let $\underline{z}$ represent the vector of data variable values available for each individual in the study. This vector may be subdivided into two parts--vector $\underline{z}_1$ representing the pre- and postnatal variable domain, and vector $\underline{z}_2$ representing all dental variables of asymmetry. Our research problem is to display the interrelatedness of the two domains measured by $\underline{z}_1$ and $\underline{z}_2$ respectively.

In the same way that factor models display the structure of relationships within a domain, the canonical model displays the structure of relationships across domains. By definition the canonical correlation is the maximum correlation between linear functions of the two vector variables $\underline{z}_1$ and $\underline{z}_2$. It is found by deriving coefficients for each of the subvectors such that a linear combination of these factor coefficients $\underline{c}$ and $\underline{d}$ with their respective variable vectors yields

two components $\underline{x}$ and $\underline{y}$, where the correlation between all N $\underline{x}$ and $\underline{y}$ components is maximized. Thus

$$\begin{aligned} \underline{x}_1 &= \underline{c}' \underline{z}_1 & \text{and} & & \underline{y}_1 &= \underline{d}' \underline{z}_2 \\ \text{where } \underline{m}_{\underline{x}} &= 0, \underline{s}_{\underline{x}}^2 = 1 & \text{and} & & \underline{m}_{\underline{y}} &= 0, \underline{s}_{\underline{y}}^2 = 1 \\ \text{and} & & R_c &= 1/N \sum_{i=1}^N \underline{x}_i \underline{y}_i & \text{max.} & \\ & & & & & 7.1 \end{aligned}$$

R_c is the maximum correlation that can be developed between a linear function of $\underline{z}_1$ and a linear function of $\underline{z}_2$.

The interpretation of the canonical factors $\underline{x}$ and $\underline{y}$, is also important--specifically, which variables contribute most to the maximally correlated components? This is given by the factor structures $\underline{s}_1$ and $\underline{s}_2$ giving the correlations between the canonical factors and the vector variables that define them. Then the variance extracted from the first domain by factor $\underline{x}$ is $(\underline{s}_1' \underline{s}_1) p_1$ where p_1 is the number of variables in $\underline{z}_1$. The redundancy of the first domain given the second, symbolized as R_{dx} , can then be computed as

$$R_{dx} = ((\underline{s}_1' \underline{s}_1) / p_1) R_c^2. \quad 7.2$$

Similarly

$$R_{dy} = ((\underline{s}_2' \underline{s}_2) / p_2) R_c^2 \quad 7.3$$

and in general $R_{dx} = R_{dy}$ --i.e. prediction of one domain from the other may be better than the prediction of the other from the one.

Additional pairs of functions that maximally correlate can usually be found subject to the restriction that

the functions in each new pair must be uncorrelated with all previously located functions in both domains. We next derive another pair of components x_2 and y_2 analogous to the first two except that they must be uncorrelated with the first pair. The analysis is then carried through steps 7.1 to 7.3 and the steps are repeated developing analogous pairs up to the lesser of p_1 and p_2 .

If n equals the total number of component pairs, the analysis will include the $p_1 \times n$ matrix $\tilde{C}$ of factor score coefficients for the first domain, the $p_2 \times n$ matrix $\tilde{D}$ of factor score coefficients for the second domain, the $p_1 \times n$ matrix $\tilde{S}_1$ and the $p_2 \times n$ matrix $\tilde{S}_2$ of factor structures for the first and second domains respectively, and the n sets of values for R_{dx} and R_{dy} . Finally the total redundancy of the first domain given the second for the rank n canonical model is given as

$$R_{d1} = \sum_{k=1}^n R_{dx_k} ;$$

Similarly
$$R_{d2} = \sum_{k=1}^n R_{dy_k} .$$

Tests of significance for the canonical correlation coefficient have been derived by Bartlett using a test statistic referred to as Wilks' Lambda. The null hypothesis that z_1 is unrelated to z_2 is tested by a function of Λ that is approximately distributed as chi-square with $p_1 p_2$ degrees

of freedom. Once the significance of R_c is established selected variables in each set are interpreted in the light of their correlation with the relevant factors as given by the factor structure.

The computation of the canonical correlation analysis involves the solution of an eigenstructure problem involving a partitioning of the correlation matrix for z_1 and z_2 as follows:

$$R = \left[\begin{array}{c|c} R_{11} & R_{12} \\ \hline R_{21} & R_{22} \end{array} \right]$$

In the present study the total correlation matrix of all variables was obtained by a computer program modified from Cooley and Lohnes (1971: 43-44). The output from this program was then used as input to the Cooley-Lohnes program entitled CANON (1971: 194-197), which computes the entire canonical analysis.

Missing Data

One final methodological problem remains to be discussed--namely, missing values for asymmetry measures where some of the antimeres were unmeasurable in a particular individual. Given the structure of the analysis, this problem affects the computation of the full correlation matrix which

is the input to the canonical program. Two solutions are possible: to replace the missing values with the mean value of the available measures, or to compute the bivariate correlation for each cell of the matrix from the available values only. Substitution of the mean value is the least appealing alternative in the present circumstances, because in some cases the number of missing values exceeds the number of values entering into the computation of the mean. The alternative is to base computations on a correlation matrix where each cell value is based on available measures only. Unequal case size for the cells of the correlation matrix means that we must choose some intermediate N for the tests of significance. Some average value seems appropriate and Rohlf (1972) recommends the use of the harmonic mean of cell size as the most conservative value under the circumstances.

It should be noted that the correlation matrix obtained under these conditions may not be positive semi definite (Rohlf, 1973). Fortunately, the problems that this could generate do not appear to affect our data.

Finally missing data may mean that the probability statements in tests only apply to the subpopulation defined by the available values. We do not believe that this affects our data since there is no a priori reason to assume that the factors determining the absence of a value are systematically

related to size and dimensional asymmetry. We conclude that the subpopulation defined by the available values, in this case, does not lose its generality with respect to the parameters of interest in the investigation.

Chapter 8

Results

This chapter which describes the results of the statistical analysis of our data is divided into two parts. The first will deal with the traditional univariate analysis of the data in terms of simple descriptive statistics. The second will report the results of the multivariate analysis using canonical correlations.

Part I

The aim of this section is to profile some of the more important interrelationships among the variables under analysis. We begin with the simple descriptive statistics that appear in Appendix I. This lists the means, variances, standard deviations, high and low values, and number of cases for the 28 variables under study. Several of these statistics require comment.

The average coefficient of consanguinity for our population is high (0.01676). This is in contrast to an average of 0.0046 reported for Japan by Schull and Neel (1965). The difference represents a sampling error which is

advantageous in the present context since it gives a large sampling of inbred individuals to study with respect to asymmetry.

The asymmetry values are also of great interest, especially in relation to their standard deviations. It is apparent for all six measures of asymmetry (Dents01, 03, 05, 07, 09, 11) that the standard deviation approximates the mean, indicating a markedly skew distribution. An examination of the appropriate frequency distributions in Appendix II clearly illustrates that most individuals have asymmetry values that fall well below the mean value of the population. It also appears that the asymmetry distributions are bimodal.

Other variables that are clearly skew are the number of conceptions, the F coefficient, the number of stillbirths, the DMF, the number of times in bed for two weeks or more, the number of convulsive attacks, and the DEF. Finally our sample is roughly equally divided between males and females.

The matrix of intercorrelations between all variables appears in Appendix III. We merely note at this point that there seem to be no significant, first order correlations among the six measures of asymmetry. Females, as might be expected, tend to have smaller dental diameters than males. We also find the set of interrelationships among the prenatal variables that we might expect from our review of the

literature. We reserve an interpretation of this complex of correlations to the multivariate approach of Part II.

As a preliminary analysis we have set up a cross tabulation of various birth weight levels with various levels of gestational age. We have chosen this particular categorization of the data because birth weight and gestational age are the two most significant parameters of prenatal stress (see chapter 4). Categorization by level of asymmetry would be inappropriate for our data since it would require a six-way analysis to be meaningful. This would divide the population into so many categories that the number of individuals in each cell would in many cases be too small to be reliable. On the other hand, if each asymmetry measure were studied individually in its relationship to the remaining variables, we would have a proliferation of comparisons based on repeated use of the same non-asymmetry values with different measures of asymmetry. Meaningful comparisons could only be made if we had six independent samples of asymmetry and non-asymmetry scores, one for each asymmetry measure used. For these reasons we have restricted our cross-tabulation comparisons to the two most important non-asymmetry variables, birth weight and gestational age. The complex of interrelationships between the various measures of asymmetry and other variables is reserved for the multivariate approach

of part II.

For each category of birth weight for gestational age we have computed the mean value of each variable, starting with maternal age. We thus have a two-way table of means for all variables. The analysis of variance on the row, column, and interaction effects have been calculated and the results are summarized below (only values significant at the 0.05 level are reported; see also Appendix IV).

As can be seen from this analysis, there is no significant association between birth weight for gestational age and mean level of asymmetry. There is no increase in asymmetry with decreasing birth weight or gestational age, though there is some evidence that size of the lower lateral incisor increases with birth weights over 351 decagrams. Other than this there is no statistically significant difference in the mean values of any of the dental parameters measured for this study, as categorized by birth weight and gestational age.

There are, however, two interesting relationships demonstrated between gestational age and mean consanguinity value and mean number of confinements for illness. A longer time span in utero is clearly associated with higher fetal coefficients of consanguinity, and the longer the child is in utero, the fewer the number of confinements for illness.

<u>Variable</u>	<u>Row</u>	<u>Column</u>	<u>Interaction</u>
1- Maternal age	--	--	---
2- No. Conceptions	--	--	--
3- Consanguinity	4.23 (F_{464}^2)	--	--
4- Sex	--	--	--
5- Mats/per	--	--	--
6- Food/per	--	--	3.11 (F_{464}^8)
7- No. Stillbirths	--	--	--
8- Dents01 (I_2^2 asym.)	----	--	--
9- Dents02 (I_2^2 size)	--	--	--
10-Dents03 (I_2 asym.)	--	--	--
11-Dents04 (I_2 size)	--	2.66 (F_{318}^4)	--
12-Dents05 (M_1^1 MD asym)	--	--	--
13-Dents06 (M_1^1 MD size)	--	--	--
14-Dents07 (M_1^1 MD asym)	--	--	--
15-Dents08 (M_1^1 MD size)	--	--	--
16-Dents09 (M_1^1 BL asym)	--	--	--
17-Dents10 (M_1^1 BL size)	--	--	--
18-Dents11 (M_1^1 BL asym)	--	--	--
19-Dents12 (M_1^1 BL size)	--	--	--
20-Age	--	--	--
21-No. Per. Teeth	--	--	--
22-DMF	--	--	2.14 (F_{464}^8)

<u>Variable</u>	<u>Row</u>	<u>Column</u>	<u>Interaction</u>
23-Bed 2 Weeks	3.00 (F_{464}^2)	--	--
24-No. Convulsions	--	--	--
25-No. Pri. Teeth	--	--	--
26-DEF	--	--	--

The significant interaction effects of birth weight and gestational age on food costs per person and number of decayed, missing, or filled teeth allows for no clear cut interpretation. We therefore conclude the preliminary analysis of the data at this point and turn to the multivariate results.

Part II

In any canonical correlation analysis multiple measures in one conceptual domain are correlated to multiple measures in some other conceptual domain. In our analysis we have grouped the 12 dental variables of size and asymmetry as one domain and the remaining 16 variables as the other. For simplicity we will refer to the former as the dental domain and the latter as the 'stress' domain.

We have chosen this division of the data because we wish to examine the effects of the 16 stress variables on the dimensional development of the teeth. The term 'stress' here is used broadly as a cover term including variables that are not measures of stress themselves but may be concomitant variables included as controls for stress variables proper.

The chi-square test of the significance of the canonical correlation coefficient discussed in chapter 7 is equivalent to the F test of the overall null hypothesis in ANOVA models. Just as a significant F justifies the further consideration

of the constituent means in the ANOVA model, a significant chi-square justifies the further interpretation of the constituent variable contributions to the canonical R_c . Table 8.1 reports the significant canonical R_c 's for our data.

<u>Canonical</u>	<u>R_c</u>	<u>R_c^2</u>	<u>Chi Square</u>	<u>N.D.F.</u>	<u>Lambda'</u>
1	0.6082	0.370	351.11	192	0.2809
2	0.4707	0.222	223.42	165	0.4457

Table 8.1. The canonical correlations and chi square tests for the first two canonicals significant at the 5% level.

In any canonical model there are as many canonical R_c 's as the number of variables in the smaller of the two sets of variables being related. This number n , is referred to as the rank of the model. In the present instance $n = 12$, the number of asymmetry and size measures in the dental domain being related to the remaining variables in the stress domain.

To understand what a canonical analysis does, we should conceptualize each canonical R_c as a highlighting of those particular characteristics in one domain that correlate highly with particular characteristics in the other. Each successive canonical R_c is independent of the previous one, so

that the various combinations of variables in interrelationship that emerge can be interpreted independently of all previous combinations. For our data only the first two canonicals are significant at the 5% level. We present the interpretations of each of these two canonicals below.

First Canonical

The first canonical R_c tells us that a particular linear combinations of variables in the stress domain can be correlated with a particular linear combination of variables in the dental domain, yielding a coefficient of correlation of 0.60. This represents the maximum degree of interrelatedness that can be developed between the two domains. No other possible linear combination of the variables could produce a higher correlation.

Our problem in reporting the results is to determine which combination of variables in each domain is responsible for this particular canonical R . This is accomplished by reference to the factor structure of each domain.

As explained in chapter 7, each individual's vector of variables scores for a domain is reduced to a single number which is a linear combination of the scores in the vector. As an example the 16 scores in the stress domain for any given individual are reduced to a single number which we call his $\underline{x}$ value, or $\underline{x}$ component. A similar reduction is made with

respect to his 12 dental scores yielding his y component. The $\underline{x}$ and y components for all individuals are then correlated to produce the canonical correlation coefficient R_c .

If all the individual values for a given variable in the stress domain were to be correlated with their corresponding x components, we would get an assessment of that variable's contribution to the determination of the $\underline{x}$ component of the stress domain. ' $\underline{x}$ ' is a linear combination of several variables. The stronger the contribution of the variable in question to this combination, the higher the correlation between that variable and $\underline{x}$.

The application of the above procedure to all 16 variables in the domain gives us the factor structure of the stress domain as reported in Table 8.2. Each value represents the bivariate correlation between that variable and the $\underline{x}$ component. The $\underline{x}$ component in turn, represents the stress domain in the canonical correlation R_c , so that indirectly the factor structure measures the importance of each variable to the inter-relatedness of the two domains.

As can be seen in Table 8.2 the stress domain variables highlighted by the first canonical are sex, SES, age, and illness history. The $\underline{x}$ component represents, in this case, older male children of higher socio-economic status (as regards household density) who reveal a slight tendency to be frequently

<u>Variable</u>	<u>Correlation</u>
1. Maternal Age	0.099
2. No. of Conceptions	0.076
3. Consanguinity	-0.008
4. Gestational Age	-0.073
5. Sex	-0.418*
6. Mats per Person	0.270*
7. Food Costs per Person	-0.017
8. No. of Stillbirths	-0.107
9. Birth Weight	0.011
10. Age	0.648*
11. No. of Permanent Teeth	0.677*
12. DMF	0.339*
13. Bed 2 weeks or more	0.247*
14. Convulsions	0.075
15. No. of Primary Teeth	-0.695*
16. DEF	-0.183

Table 8.2. Factor structure of the stress domain for the first canonical ($R_c = 0.60$). Each value represents the bivariate correlation between the variable in question and the $\underline{x}$ component of the stress domain.

*correlations above 0.2 are starred.

ill. Because they are older they have fewer primary and more permanent teeth.

The corresponding factor structure for the dental domain is given in Table 8.3. It indicates that the y component represents individuals with larger upper lateral incisors and large mesio-distal diameters of the upper and lower first permanent molars. Such individuals tend to have more asymmetrical buccolingual dimensions of the lower first molar associated with a slight tendency for these diameters to be small.

Given this interpretation of the factor structures, the canonical correlation of 0.60 indicates that size aspects of the dentition show a clearcut sex influence, and that this difference is most clearly manifest in the older children of our sample. There is also some indication that bucco-lingual size asymmetry of the lower first molar is associated with these older males (see Table 8.4 for a summary).

To place these interrelationships into perspective, however, we must ask ourselves to what extent can the variance in one domain be explained by the variance in the other. In short, what is the redundancy between domains, or what is the predictive value of the relationship under discussion? Our analysis reveals that only 4% of the variance in the stress domain can be predicted from the dental domain, and conversely

<u>Variable</u>	<u>Correlation</u>
1 -- I^2 asy.	-0.097
2 -- I^2 size	0.516*
3 - I_2 asy.	-0.077
4 - I_2 size	-0.089
5 - M^1 MD asy.	0.024
6 - M^1 MD size	0.542*
7 - M_1 MD asy.	0.074
8 - M_1 MD size	0.588*
9. - M^1 BL asy.	0.030
10 - M^1 BL size	-0.001
11 - M_1 BL asy.	0.251*
12 - M_1 BL size	-0.118

Table 8.3. Factor structure of the dental domain for the first canonical ($R_c = 0.60$). Each value represents the bivariate correlation * between the variable in question and the y component of the dental domain.

* correlations above 0.2 are starred.

<u>Stress domain</u>		<u>Dental domain</u>	
Sex	-0.418	i^2 size	0.516
Mats Per Person	0.270	M^1 MD size	0.542
		M_1 MD size	0.588

Age	0.648	M_1 BL asy.	0.251
No. of Permanent Teeth	0.677		
DMF	0.339		
No. of Primary Teeth	-0.695		
Bed 2 weeks or more	0.247		

Table 8.4. Interrelationships between important elements of the factor structures of the stress and dental domains for the first canonical ($R_c=0.60$).

only 3% of the dental variance is explained by stress variance. Thus although we have a statistically significant relationship, the biological relationships are of a very small order.

Second Canonical

A. Factor structure for the stress domain

Table 8.5 indicates that the x component largely represents older children of poor socio-economic status, who were late born with respect to gestational age, and whose mothers were young and likely to be primiparas at the child's birth.

B. Factor structure for the dental domain

Table 8.6 indicates that the y component consists by and large of individuals with small dental diameters, especially if that diameter is also associated with greater asymmetry. The incisors and the bucco-lingual aspects of the first molars seem to parallel each other in this respect and contrast with the mesio-distal diameters of the first molars. The latter tend to be large when the former are small. Of particular interest is the fact that high asymmetry is associated with small size in the upper lateral incisors, but small size of I_2 is not accompanied by greater asymmetry for this tooth.

<u>Variable</u>	<u>Correlation</u>
1 - Maternal Age	-0.215*
2 - No. of Conceptions	-0.169
3 - Consanguinity	0.053
4 - Gestational Age	0.950*
5 - Sex	-0.095
6 - Mats per Person	-0.158
7 - Food Costs per Person	-0.327*
8 - No. of Stillbirths	-0.192
9 - Birth Weight	0.147
10 - Age	0.568*
11 - No of Permanent Teeth	0.085
12 - DMF	-0.104
13 - Bed 2 weeks or more	-0.028
14 - Convulsions	0.082
15 - No. of Primary Teeth	0.075
16 - DEF	-0.229*

Table 8.5. Factor Structure of the stress domain for the second canonical ($R_c = 0.47$). Each value represents the bivariate correlation* between the variable in question and the x component of the stress domain;

*correlations above 0.2 are starred.

<u>Variable</u>	<u>Correlation</u>
1 - I^2 asy.	0.269*
2 - I^2 size	-0.687*
3 - I_2 asy.	0.058
4 - I_2 size	-0.268*
5 - M^1 MD asy.	0.133
6 - M^1 MD size	0.247*
7 - M_1 MD asy.	0.135
8 - M_1 MD size	0.260*
9 - M^1 BL asy.	-0.054
10 - M^1 BL size	-0.332*
11 - M_1 BL asy.	0.209*
12.- M_1 BL size	-0.358*

Table 8.6. Factor structure of the dental domain for the second canonical ($R_c = 0.47$). Each value represents the bivariate correlation* between the variable in question and the y component of the dental domain.

*correlations above 0.2 are starred.

C. Relationships between domains

Table 8.7 summarizes the following relationships between domains: small teeth with high asymmetry are found in the older children of our sample; such children are characterized as of lower socio-economic status, late born with respect to gestational age, and the first child of a young mother.

D. Redundancy pattern

Only 1.1% of the variance in the stress domain can be predicted from dental variance, and only 2% of dental variance can be explained by stress variance. We conclude that though statistically significant the interrelationships discussed in 'C' above are biologically very small.

In the following chapter we shall discuss the meaning of these results in the perspective of the literature review in the early chapters.

<u>Stress domain</u>		<u>Dental domain</u>	
Maternal Age	-0.215	I^2 asy.	0.269
(No. of Conceptions	-0.169)	I^2 size	-0.687
Food Costs per Person	-0.327	I_2 size	-0.268
Age	0.568	M^1BL size	-0.332
		M_1BL asy.	0.209
		M_1BL size	-0.358

Gestational Age	0.350	M^1MD size	0.247
DEF	-0.229	M_1MD size	0.260

Table 8.7. Interrelationships between important elements of the factor structures of the stress and dental domains for the second canonical ($R_c = 0.47$).

Chapter 9

Discussion

In this chapter we shall discuss our results in the framework of what we consider to be the major findings that have emerged from our analysis. These may be outlined as follows:

- (1) There is a small but significant relationship between variables that can be interpreted as indicating pre- and postnatal stress on the one hand, and asymmetry on the other.
- (2) The effects of these stress variables are most pronounced on asymmetry of the mesiodistal diameter of the upper lateral incisor and the buccolingual diameter of the lower first molar.
- (3) Smaller dental diameters are also associated with stress variables referred to in (1) and (2) above, and the effects on size seem more pervasive, affecting mesiodistal diameters of both upper and lower lateral incisors and buccolingual diameters of both upper and lower first molars.
- (4) The etiology and nature of asymmetry in I^2 and M_1 suggests

that asymmetry in the dentition is an outcome of a complex of factors besides stress. These include important 'field' effects limiting the extent of susceptibility in terms of the length of time the respective teeth are vulnerable, and in terms of which aspects of the tooth are susceptible.

(5) There appear to be no relationships between the stresses associated with asymmetry and measures of postnatal morbid risk.

(6) There appears to be no relationship between degree of inbreeding and asymmetry.

(7) There appears to be no relationship between sex and asymmetry.

All of these points must be understood to be tentative conclusions based on an analysis which we believe to be basically heuristic. The limitation of the canonical approach is that its factors must be interpreted. Their meaning can not be framed in the simpler yes or no terms of traditional testing based on a simple null hypothesis. With this limitation in mind, we shall consider the conclusions outlined above in what follows.

Stress Variables Association with Asymmetry

A. Fetal growth rate and asymmetry

One of the major arguments developed in the earlier

chapters of this study is that fetal growth rate is the most practical and useful index of prenatal stress. Operationally fetal growth rate was defined as birth weight for gestational age. The preliminary analysis of the data embodied in the study of variable means as cross-tabulated for different levels of birth weight and gestational age indicates that prenatal stress as defined is not significantly associated with level of asymmetry. Similarly the canonical analysis of the data in Tables 8.4 and 8.7 show that birth weight and gestational age considered jointly to not make a significant contribution to either canonical R_c .

In spite of this lack of direct evidence for prenatal stress effects as defined, we note that in our sample decreasing gestational age is significantly associated with greater postnatal morbid risk and that there is also indirect evidence for inbreeding depression in fetal growth rate, a matter which we shall elaborate on shortly. We consider these points as evidence of the basic correctness of the hypothesis that fetal growth rate is an important parameter in prenatal stress. Apparently in our sample fetal growth retardation as measured by birth weight for gestational age cannot sufficiently reduce the heterogeneity of birth weight variance which was discussed in chapter five. Fortunately, fetal growth rate can be measured by other indirect evidence.

The indirect evidence we speak of is based on what can be considered a parallel between our results and those of recent studies of inbreeding depression on fetal size in mice. McCarthy (1968) has found that inbreeding depression of fetal weight in mice is marked between inbreds and controls sacrificed at 17 1/2 days gestation, but that no inbreeding depression was manifest in birth weight. He explains the lack of inbreeding depression in the latter by the assumption that time span in utero is to some extent a function of fetal size. Because of their retarded development inbred mice spend more time in utero than outbreds, during which time they catch up in birth weight. We note that in our sample gestational age is an important factor in the second canonical (see Table 8.7), but it shows no concomitant relationship with birth weight. We also note that inbred children in the sample spend significantly more time in utero than outbreds, though they do not differ markedly in birth weight. The parallel with the mouse data is strong, suggesting that time span in utero beyond 40 weeks is no longer correlated with weight at birth.

If the salient feature determining gestational age in the cases cited is fetal size, we may generalize and speculate that in our sample infants deficient in prenatal growth for whatever reason spend more 'catch up' time in utero and thus show little difference in size at birth from normal infants born at term.

With respect to asymmetry, however, the critical phases of dental growth for such retarded children were passed in a state of deficiency, so that stress may still be manifest in the dental characteristics despite normal birth weights. In short, the key stress that produces asymmetry is, in our opinion, fetal growth retardation--but the relevant measure of IUGR is not directly ascertainable by birth weight for gestational age in our sample.

B. Fetal growth retarding factors

Possible causes of growth retardation and asymmetry are revealed by a further consideration of the stress domain in the second canonical (Table 8.7). Asymmetric children tend to have young primiparous mothers and come from households with relatively low food costs per person. The relationship between primiparity and immaturity at birth were considered fully in chapter five and we need not repeat the details here. For reasons not fully known but probably related to inefficiency of placental circulation, first born children are significantly lighter and more immature at birth than their subsequent siblings. Thus the association between primiparity and asymmetry is a clear indication of the effects of prenatal stress.

The socioeconomic factor in our sample may not be similarly interpretable. As we shall discuss shortly,

asymmetry in the individuals under consideration involves both early and late developing teeth--i.e. teeth whose dimensions are determined prenatally and those whose size are believed to be set after birth. The pre- or postnatal source of the stresses leading to such asymmetry is a point of considerable theoretical importance. Unfortunately, it is impossible to attribute the socio-economic stresses in our sample to either the prenatal or the postnatal period of development exclusively. The problem is to determine if our measures of SES have reference to the prenatal period of the children in question, or if they have exclusive reference to the period of data collection, six to 12 years later.

For a Japanese sample comparable to our own, Bailit et al. (1968) considered it probable that the same conditions of socioeconomic status characterized a child's family at its birth as at the time of data collection, some years later. As we argued earlier (chapter 7) this view is not consistent with the secular trend toward increasing birth weight concomitant with the economic recovery of postwar Japan (Gruenwald et al., 1967). However, economic improvements following the war may not have changed the relative statuses of families during the course of the recovery. In that case SES levels recorded for our sample would reflect the relative economic circumstances affecting the mother's pregnancy for

children of any fixed age group. Our data was not analyzed by age group, nor does this seem called for a posteriori since the underlying premise is itself hypothesis. We conclude that the problem remains unresolved for our data.

Of relevance to some of the issues just considered is the remaining significant variable in the stress domain of the second canonical, age of the child. Greater asymmetry in older children may indicate greater random differentiatial wear between left and right antimeres as a function of age. Alternatively, it may have reference to secular differences in economic conditions of stress as discussed above. Wartime and early postwar economic circumstances were not as favorable as conditions following the postwar economic recovery. Just as Japanese birth weights reflect this difference, so may the strong age component of asymmetry in our sample.

In this case also, the relationship of SES to this age component is ambiguous. It is empirically impossible to decide if the canonical should be interpreted as indicating two separate and independent factors or not. If the latter alternative is correct differences in SES only have an effect on the older children of the sample. Two separate and independent factors would indicate that SES has an effect on asymmetry that cuts across all age groups and that older children are more asymmetrical in addition to any direct

effects of SES.

Both points of view have merit. It is conceivable, for example, that differences in the nutritional status of the mother only affect the fetus if the nutritional level is below a critical threshold--the fetus being buffered from the contingencies that affect the mother in all but the most extreme cases. On the other hand, the existence of such a threshold is hypothetical, and a continuous effect of food costs per person can not be discounted a priori. The issue remains unresolved until we have further evidence.

Aspects of the Dentition Associated with Asymmetry and Stress

A. Asymmetry and developmental timing

The mesiodistal diameter of I^2 and the buccolingual diameter of M_1 appear to be particularly susceptible to the stresses that we presume to be responsible for asymmetry. At the same time we find that the effects of stress on size per se is extensive, affecting I^2 and I_2 mesiodistally and M^1 and M_1 buccolingually. To understand these results we must consider the pattern of development of the human dentition and of these four teeth in particular.

Initiation of odontogenesis in I_2 and M_1 both begin in utero (3 1/2 - 4 months for M_1 and 5 - 5 1/2 months for I_2). The size and shape of a tooth are finally determined by the time of apposition of enamel and dentin which begins at birth

for M_1 , 10-12 months for I^2 , and 3-4 months for I_2 (Schour and Massler, 1940). As a consequence we may characterize M_1 and I^2 as early and late developing teeth respectively.

Furthermore, this timing differential may be the important element of the developmental pattern determining differential susceptibility between M_1 and I^2 . Between initiation of odontogenesis to the apposition of enamel and dentin, M_1 is exposed to potential stress for a much more limited period of time than is I^2 . Perhaps in this context the concept of the late developing tooth should be replaced by the notion of the slow maturing one. We note, however, that this notion does not account for the observed difference in vulnerability between buccolingual and mesiodistal diameters of M_1 . To the extent that both the upper lateral incisor and the first lower molar begin formation well within the fetal period, both are exposed to the prenatal stresses discussed in the previous section, including any prenatal effects of poor SES. The molars, however, are not exposed to the postnatal influences to which I^2 is subjected for the first year of life. There is thus an additional possible postnatal effect of SES on incisor development.

It follows that the data allow for two plausible interpretations of the source of the stresses producing asymmetry in I^2 ; either (1) the stresses are strictly postnatal

involving socioeconomic variables only (the age component being understood as an SES variable in this context); or (2) the stresses are both pre- and postnatal where SES may be either (a) excluded or (b) included in the list of prenatal as well as postnatal factors.

Although it is impossible to choose between these alternatives on the basis of the data, there are several points which are relevant to their interpretation. There is a substantial body of evidence indicating that factors limiting late developing teeth are cumulative effects operating over a large span of the life cycle preceding the development of the tooth. Thus third molar size in inbred strains is smaller than in hybrids because of maternal influences independent of fetal genotype (Grueneberg, 1951). Also third molar agenesis in mice has been shown to be more common in first born and in early litters of young mothers than in controls (Searle, 1954a; 1954b)--again indicating long-lasting effects of the maternal environment. Similarly third molar agenesis in man is frequently accompanied by reduction in the size of the dentition as a whole (Garn et al, 1961; 1963; 1964), evidence of early and pervasive deleterious influences the causes of which are not yet understood. We are inclined to accept the argument for the existence of both pre and postnatal effects on I^2 as a consequence.

B. Asymmetry and 'Field' theory

Other important differences in response to asymmetry characterize I^2 and M_1 . Bailit et al. (1970) argue that some weighted measure of asymmetry might be called for if there is a differential susceptibility in the dentition to the stresses producing asymmetry. We have already seen that only I^2 and M_1 exhibit asymmetry as a function of stress. The data indicate that in the former stress affects the mesiodistal diameter and in the latter the buccolingual aspect. The pattern of this observed differential vulnerability suggests the following explanation.

Van Valen has argued that one function of Butler's 'field' effect is to control total tooth row length as it deviates from the mean in one or both directions in the course of development (1962a). The greater environmental component in the later developing teeth of a class could provide the flexibility to produce this control. We would expect under the circumstances that only aspects of a 'distal' tooth contributing to row length would be susceptible, and this is consistent with our findings. We observe asymmetry in I^2 but not I_2 , the latter being the stable tooth in the lower incisor field. The first molar is the key tooth in the molar row and we would not expect asymmetry in its mesio-distal aspect, but its buccolingual dimension would be free to vary

since it is not an element of row length. M_1 for our data is likewise consistent with this assumption, although we can think of no reason why the asymmetry in the bucco-lingual dimension of M_1 is not paralleled in M^1 . We would conclude that asymmetry of antimeres in a morphological class is determined by a complex developmental process conditioned by the total developmental pattern of the class--thus asymmetry in different structures of the body can not be assumed to be a simple function of the overall stresses impinging on the organism (cf. Reeve, 1960; Van Valen, 1962).

To further support this conclusion we may consider the relationship between tooth agenesis in man and asymmetry. The absence of a tooth clearly affects the total class row length and if Van Valen (1962) is correct it should affect the growth relationships between the remaining teeth in the class. Sofaer et al. (1970) have found that such compensatory interaction between developing teeth leads to increased size of the remaining teeth on a side where there has been unilateral extreme reduction or absence of one of the members of the class. The outcome for their study was asymmetry of the central incisors in cases of unilateral absence or pegging of I^2 . Both agenesis and, as a consequence, asymmetry were considered to be functions of a poor developmental environment since the total incisor field was significantly smaller than normal.

Our point is that agenesis or extreme reduction in size (pegging in I^2) is only common in the unstable tooth of the class. It is virtually unknown in M_1 for example. As a consequence buccolingual asymmetry in M_1 does not appear to be conditioned by the developmental pattern of tooth row length as in I^2 . In this respect, therefore, asymmetry in the two teeth is not comparable.

C. Asymmetry and Agenesis

There is one remaining similarity between asymmetry and agenesis that should be considered. Recent studies have shown an interrelationship between third molar and I^2 agenesis which suggests a similar or common underlying genetic mechanism behind both. One possibility is a threshold model based on the assumption of a major gene. In this model the genetic expression of agenesis is conditioned by the epigenetic background of the developing organism. One element of this epigenetic system is a general reduction in the size of the teeth.

It is clear from the second canonical (Table 8.7) that the dental domain includes a general reduction in the size of the teeth. The parallels with agenesis are worth specifying. First in both asymmetry and agenesis only certain teeth appear to be susceptible; and second, in both, penetrance seems dependent on an epigenetic background including

a general reduction in the size of the teeth. We shall return to a consideration of a threshold model for asymmetry in the concluding chapter. We would merely point out at this time that if the model proves applicable, our results include prima facie evidence that size reduction in the teeth is an indication of an inadequate epigenetic background for the developing dentition.

Important Negative Findings

Garn et al. (1966; 1967) found that asymmetry was greater in males than in females and attributed their findings in this respect to a genuine sex difference in susceptibility to asymmetry. We, in contrast, find no great sex differences in asymmetry and are supported in this conclusion by the work of Bailit et al. and Adams and Niswander (1965). It is true that males seem to be particularly affected by the 'stress'/dental interrelationships of the first canonical (Table 8.4). That dental domain, however, basically highlights size rather than asymmetry aspects of the dentition and we suspect that the first canonical merely affirms that males tend to have larger teeth than females. Further, the observed relationships between sex and asymmetry reported by Garn and coworkers may be nothing more than a corollary of the relationship between size and asymmetry. In their sample larger teeth tended towards greater asymmetry and males had larger teeth.

We also argue that greater asymmetry in larger teeth is biologically deceptive at face value. Garn et al. used no appropriate transformation of the data to account for the greater biological significance of a given degree of asymmetry in a small tooth as compared to a large one. The significance of such a correction is manifest in the second canonical (Table 8.7) where we find asymmetry negatively correlated with size in contrast to the results of Garn et al. (1966; 1967).

The two remaining points to be discussed in this section are the lack of any significant component of postnatal morbid risk associated with asymmetry, and the lack of any demonstrable inbreeding effect on the level of asymmetry. The former might be a function of the inadequacies of the measures of risk available for the data. As was discussed in chapter 7 only frequency of serious illness was monitored in the original ABCC study, not the kind of illnesses involved. The results here are thus equivocal. In contrast the lack of any inbreeding effect cannot be attributed to methodology and seems to spring directly from the data.

Two sources of shock to the developing organism are postulated in the relevant asymmetry literature. First are environmental stresses such as nutritional deprivation or disease. Second are genetic stresses which break down the

coadaptation of the genetic system, such as inbreeding in normally cross-fertilizing species, or mutations. The evidence supporting the existence of these relationships is substantial (see chapter 2), yet in terms of our results only a small though statistically significant linear dependence of asymmetry on the degree of environmental stress was demonstrable. Even in this respect at most 2% of size and asymmetry variance in our sample was related to the environmental variance in our stress domain.

Bader has shown that environmental influences may account for as much as 16-27% of tooth size variance in mice. If similar estimates hold for man, there is a sense in which the negativeness of our findings with respect to inbreeding variance carries over to the positive findings with respect to environmental variance. Inbreeding may be one of many poor prognosticators of asymmetry, albeit an especially poor one. We shall elaborate on this argument in our conclusion, for in our opinion the poor predictability of asymmetry from stress variables points to one of the most important characteristics of asymmetry in the context of developmental theory.

Chapter 10

Conclusions

From the theoretical perspective, the present study is fundamentally centered on the concept of developmental stability, of which asymmetry is presumably a measure. Developmental stability is in turn related to Waddington's concept of 'canalization' of the phenotype, a notion which serves to integrate the ontogenetic processes of development with the evolutionary processes operating at the population level. Simply put, the developmental events which lead to canalization function to make the expression of the phenotype homogeneous over a wide range of underlying genotypes for some optimum value! Whereas a simple linear relationship between phenotype and genotype could only maximize the frequency of optimally adapted individuals by sacrificing underlying genetic variability, canalizing mechanisms maximize adapted phenotypes without loss of genetic flexibility. They are clearly of great evolutionary significance.

At the individual level canalization processes involve plastic responses toward a fixed end determined by the needs of the population. The measure of their success at

the population level is a function of the frequency of individuals whose genotypes provide the necessary flexibility to stabilize the phenotype around the population norm. The utility of fluctuating asymmetry as a measure of the process is that the optimum value is established a priori and is the same for all bilaterally symmetrical traits and in any population, regardless of its conditions. It allows for the comparison of otherwise incomparable entities.

The advantages of the asymmetry measure, however, are not without limit. In our opinion one of the chief reasons for the small percentages of asymmetry explained by our stress domain is that the distribution of asymmetry parallels that of the canalized trait it measures. Asymmetry in this study was taken as the absolute difference between sides. With respect to the teeth most individuals have zero or a very small degree of difference between antimeres, and therefore the distribution of absolute asymmetry tends to be highly skew. This means that considerably more than half the population have values of asymmetry below the population average. Values above the mean are rare and become increasingly infrequent as asymmetry becomes greater. Similarly for any canalized trait, the bulk of the population will exhibit the optimum phenotype, and only a small percentage will fall outside the zone of canalization.

This parallel in distribution might well explain why studies which compare populations at different levels of stress find significant differences in mean asymmetries, and why attempts to correlate these two phenomena within a population yield meager results. In the canalization model populations which differ in their degree of adaptation to the environment will differ in the frequency of individuals who fall outside the canalized zone. For asymmetry this would mean a greater frequency in the higher tail of the distribution for a less well adapted group. It would also mean a higher average asymmetry for the population since there is a greater weighting of higher asymmetry values because of their more frequent occurrence. Similarly populations which are genetically identical but subjected to different degrees of environmental stress, will also exhibit differences in their mean asymmetry value as stress pushes borderling genotypes over the canalization threshold.

On the other side, since the observed homogeneity of asymmetry masks the underlying variability of genotypes within the zone of canalization, the correlation between asymmetry and stress will be weak. Almost all individuals will have the same asymmetry value regardless of stress level and the correlation coefficient will be lowered because of the unpredictable scatter of stress against asymmetry.

To illustrate the point we may cite the work of Bailit et al. 1970 (see chapter 2). In this study a significant difference in mean asymmetry was demonstrated between four populations ranked by level of stress. At the same time an attempt to correlate asymmetry and the coefficient of consanguinity within the population of Tristanites proved fruitless.

It should be noted that Bailit and co-workers specifically discounted a threshold effect for their data because their measure of asymmetry was normally distributed. However, their asymmetry score for an individual was a composite score in some sense sumative over all pairs of antimeres measured. To the extent that the level of asymmetry in one set of antimeres is independent of that in any other pair, a sumative measure might be expected to be normally distributed by the central limit theorem. In contrast our conclusions are in agreement with those of Adams and Niswander (1967) who working with asymmetry of the lower first molar alone concluded that a threshold model might be appropriate for asymmetry.

A second possible explanation for the low level of predictability between stress and asymmetry can not be discounted--namely that our stress domain does not adequately sample the relevant environmental factors affecting the teeth. Birth weight was chosen as the logical measure of fetal development because it is the single most important prognosticator of

infant health status and thus a major index of prenatal stress. The difficulty with using birth weight as an index of stress is that low birth weight children represent a very heterogeneous sample with respect to the maternal factors determining low birth weight. We attempted to reduce this heterogeneity by adjusting for such parameters as gestational age, parity, maternal age, and sex. Our failure to explain the observed 2% of the dental variance in terms of birth weight may represent a failure of these parameters to account for the significant heterogeneity in birth weight variance affecting dental development.

There are many important maternal variables not included in this analysis, such as nutritional quality, mother's prepregnant weight, mother's pregnancy weight gain, mother's height and others. They clearly affect fetal development and might account for the absence of a birth weight effect on asymmetry. However, we hypothesize in particular that the effects of maternal factors on birth weight are dependent on their effects on uterine and placental circulation. Siegel and Smookler (in manuscript) in a recent study of dental asymmetry in offspring of pregnant rats exposed to audiogenic stress, produced marked increases in asymmetry under controlled conditions (up to 35%). We speculate that the effect was produced by reduced circulation to the placenta induced in this

case by fear and anxiety. Unfortunately the authors give no data on birth weights. Nonetheless their results indicate that our basic premise of a relationship between prenatal stress and asymmetry is tenable and we suggest that the significant parameter in terms of prenatal dental stress may be placental circulation as it limits fetal size.

To summarize, our results indicate that asymmetry may parallel canalized traits in important respects, implying an inherent limitation in the study of asymmetry by correlational methods. Should this be corroborated by further research the usefulness of asymmetry for studying the ontogenetic effects of various environmental or genetic shocks on the developing human organism will have to be framed in terms of population comparisons. This is a severe limitation in view of the difficulty in controlling experimental conditions with human subjects. As a result the relevance of asymmetry as a measure of adaptedness in the individual may be difficult to determine, but it will be relatively easy to compare adaptedness of different populations by contrasting their mean level of asymmetry.

We feel justified in this latter conclusion by the statistical significance of the relationship between environmental stress and asymmetry for our sample. In spite of the poor predictability of asymmetry from stress, we have

demonstrated the following important relationships. First, asymmetry in I^2 and M_1BL is associated with children of young primiparas, with children who spend longer time spans in utero, and with children whose families are characterized by low food expenditures per person. Second, smaller diameters in I_2 and M_1BL are associated with the variables listed above including asymmetry of I^2 and M_1BL .

From these relationships we hypothesized that the expression of asymmetry is limited by two factors: First are 'field' effects as they stabilize total row length for the morphological class. Only the late developing tooth in the class will be susceptible to asymmetry of a diameter participating in row length--hence asymmetry in I^2 but not I_2 . Alternatively, asymmetry in a stable tooth will only be manifest in a diameter not related to tooth row length as in the buccolingual diameter of M_1 . Second, the expression of asymmetry in I^2 , MD and M_1BL is conditioned by epigenetic factors which also manifest themselves in small diameters for I_2MD and M_1BL and parallels in some respects the epigenetic conditions affecting the penetrance of M_3 and I^2 agenesis.

The following two lower level testable hypotheses follow from these conclusions: (1) Pegging in I^2 (the extreme in size reduction) should be associated with high asymmetry in M_1BL and with small I^2 's and buccolingual diameters

of M1; and (2) Agenesis of I_2^2 or M3 should be found with high asymmetry in M_1BL and small I_2 's and buccolingual diameters of M1. Both of these hypotheses can be easily tested by comparisons of mean size and asymmetry in easily defined populations--e.g. pegged vs. non-pegged, or agenesis vs. non-agenesis. In general comparisons of mean asymmetry between populations defined by qualitative differences in aspects of the dentition should present little difficulty.

Perhaps the most important contribution of heuristic multivariate analysis is the generation of such easily tested lower level hypotheses derived from higher level abstractions. If they are properly derived, their verification can generate a more general theory. Hopefully we have contributed to the generation of such a theory for the development of the human dentition.

Appendix I

**Table of descriptive statistics for the 28 variables
included in the study.**

DESCRIPTIVE STATS PROGRAM

MEANS, VAR., ETC. OF B

***PAGE 1 OF FILE D1

POSITION	1	2	3	4	5	6
LABEL	MEAN	VAR.	S.D.	LOW	HIGH	N
1 MAT.AGE	27.24425	24.01762	4.90078	17.00000	42.00000	479.00000
2 NO.CONCP	2.72443	2.87788	1.69643	1.00000	12.00000	479.00000
3 CONSANG.	0.01676	0.00065	0.02559	0.0	0.06250	479.00000
4 GEST.AGE	40.13570	4.88322	2.20980	29.00000	48.00000	479.00000
5 SEX	1.50522	0.25050	0.50050	1.00000	2.00000	479.00000
6 MATS.PER	3.44276	4.30780	2.07552	0.0	18.20000	479.00000
7 FOND.PER	2.95865	1.07689	1.03773	0.0	7.00000	479.00000
8 NO.STLB	0.25678	0.34187	0.58470	0.0	6.00000	479.00000
9 BIRTH.WT	303.37769	1599.65820	39.99573	120.00000	430.00000	479.00000
10 DENTS01	457.16406	156504.75000	395.60693	0.0	2119.00000	238.00000
11 DENTS02	68.52141	41.10249	6.41112	43.89999	87.39999	238.00000
12 DENTS03	347.60962	92881.68750	304.76489	0.0	1910.00000	333.00000
13 DENTS04	60.89398	16.25806	4.03213	48.89999	70.89999	333.00000
14 DENTS05	367.12354	92102.06250	303.48315	0.0	1677.00000	202.00000
15 DENTS06	101.96086	48.75366	6.98238	85.00000	124.89999	202.00000
16 DENTS07	339.22778	74299.68750	272.57959	0.0	1251.00000	272.00000
17 DENTS08	101.80551	75.20628	8.67216	81.89999	121.89999	272.00000
18 DENTS09	499.47559	205845.18750	453.70166	0.0	3746.00000	351.00000
19 DENTS10	62.10539	21.39142	4.62509	46.39999	75.89999	351.00000
20 DENTS11	564.99731	219679.68750	468.69995	0.0	2696.00000	366.00000
21 DENTS12	54.75108	21.09178	4.59258	40.89999	69.89999	366.00000
22 AGE	105.49477	201.87817	14.20838	69.00000	134.00000	479.00000
23 NO.PER.T	12.96868	24.52412	4.95218	2.00000	28.00000	479.00000
24 DMF	1.07516	1.69308	1.30119	0.0	10.00000	479.00000
25 BED.2.WK	0.29019	0.37796	0.61478	0.0	6.00000	479.00000
26 CONVULNS	0.12317	0.17517	0.41854	0.0	3.00000	479.00000
27 NO.PRY.T	10.02505	22.94917	4.79053	0.0	20.00000	479.00000
28 DEF	6.38445	14.63110	3.82506	0.0	19.00000	463.00000

PBYO,

IN=B,

ROW=GEST.AGE/-4,

COL=BIRTH.WT/-55

Appendix II

Frequency distributions of Dents 01, 03, 05, 07,
09, and 11. See table 7.3 for variable definition.

DESCRIPTIVE STATS PROGRAM

VARIABLE 10, DENTS01,

FROM DATA FILE

B

ALL

LOW	HIGH	N	PCT	CUM
0.0	0.0	21	9	9
0.0	0.0			
0.0	0.0			
114.00	114.00	1	0	9
122.00	152.00	50	21	30
155.00	162.00	7	3	33
0.0	0.0			
0.0	0.0			
253.00	273.00	10	4	37
277.00	298.00	17	7	45
307.00	327.00	10	4	49
344.00	357.00	5	2	51
382.00	384.00	2	1	52
402.00	419.00	10	4	56
431.00	454.00	8	3	59
458.00	563.00	23	10	69
579.00	671.00	20	8	77
680.00	779.00	19	8	85
800.00	896.00	10	4	89
909.00	1000.00	7	3	92
1069.00	1121.00	3	1	94
1133.00	1158.00	2	1	95
1292.00	1313.00	2	1	95
1391.00	1442.00	5	2	97
1473.00	1473.00	1	0	98
1586.00	1586.00	1	0	98
0.0	0.0			
0.0	0.0			
1941.00	1967.00	2	1	99
2076.00	2119.00	2	1	100

MISSING DATA 241.

GOOD N 238.

MEANS 457.1638

VARIANCES 156504.7500

S.D. 395.6069

DESCRIPTIVE STATS PROGRAM

VARIABLE 12, DENTS03,

FROM DATA FILE

B

ALL

LOW	HIGH	N	PCT	CUM
0.0	0.0	54	16	16
0.0	0.0			
0.0	0.0			
0.0	0.0			
0.0	0.0			
0.0	0.0			
145.00	162.00	48	14	31
165.00	183.00	51	15	46
186.00	198.00	2	1	47
0.0	0.0			
0.0	0.0			
0.0	0.0			
281.00	298.00	9	3	49
303.00	322.00	24	7	56
327.00	344.00	20	6	62
350.00	451.00	16	5	67
458.00	540.00	45	14	81
571.00	655.00	17	5	86
666.00	763.00	18	5	91
775.00	845.00	6	2	93
870.00	953.00	8	2	95
1000.00	1072.00	7	2	98
1086.00	1158.00	2	1	98
1262.00	1262.00	1	0	98
1292.00	1358.00	2	1	99
1457.00	1457.00	1	0	99
1563.00	1563.00	1	0	100
0.0	0.0			
0.0	0.0			
1910.00	1910.00	1	0	100

MISSING DATA 146.

GOOD N 333.

MEANS 347.6094

VARIANCES 92881.0000

S.D. 304.7639

DESCRIPTIVE STATS PROGRAM

VARIABLE 14, DENTS05,

FROM DATA FILE

B

ALL

LOW	HIGH	N	PCT	CUM
0.0	0.0	18	9	9
0.0	0.0			
0.0	0.0			
86.00	97.00	19	9	18
98.00	114.00	18	9	27
0.0	0.0			
169.00	169.00	1	0	28
178.00	192.00	15	7	35
196.00	212.00	14	7	42
0.0	0.0			
248.00	269.00	3	1	44
271.00	292.00	9	4	48
298.00	317.00	12	6	54
324.00	342.00	4	2	56
354.00	367.00	4	2	58
379.00	454.00	21	10	68
456.00	540.00	20	10	78
566.00	625.00	11	5	84
638.00	710.00	7	3	87
721.00	800.00	7	3	91
808.00	887.00	5	2	93
901.00	978.00	5	2	96
990.00	1010.00	3	1	97
0.0	0.0			
1156.00	1230.00	4	2	99
0.0	0.0			
1384.00	1384.00	1	0	100
0.0	0.0			
0.0	0.0			
1677.00	1677.00	1	0	100

MISSING DATA 277.

GOOD N 202.

MEANS 367.1235

VARIANCES 92100.8750

S.D. 303.4812

DESCRIPTIVE STATS PROGRAM

VARIABLE 16, DENTS07,

FROM DATA FILE

B

ALL

LOW	HIGH	N	PCT	CUM
0.0	0.0	30	11	11
0.0	0.0			
0.0	0.0			
82.00	90.00	10	4	15
92.00	113.00	39	14	29
116.00	116.00	1	0	29
0.0	0.0			
169.00	180.00	6	2	32
183.00	202.00	19	7	39
204.00	219.00	15	6	44
229.00	248.00	4	1	46
257.00	262.00	3	1	47
273.00	292.00	14	5	52
298.00	314.00	16	6	58
317.00	336.00	7	3	60
341.00	396.00	9	3	64
408.00	460.00	14	5	69
465.00	518.00	21	8	76
523.00	582.00	20	7	84
588.00	638.00	8	3	87
645.00	682.00	8	3	90
708.00	762.00	9	3	93
814.00	816.00	2	1	94
833.00	878.00	3	1	95
887.00	923.00	3	1	96
969.00	981.00	2	1	97
1021.00	1053.00	2	1	97
1072.00	1129.00	5	2	99
1165.00	1165.00	1	0	100
1251.00	1251.00	1	0	100

MISSING DATA 207.

GOOD N 272.

MEANS 339.2278

VARIANCES 74298.6250

S.D. 272.5776

DESCRIPTIVE STATS PROGRAM

VARIABLE 18, DENTS09,

FROM DATA FILE

B

ALL

LOW	HIGH	N	PCT	CUM
0.0	0.0	40	11	11
0.0	0.0			
0.0	0.0			
0.0	0.0			
139.00	165.00	57	16	28
168.00	190.00	20	6	33
215.00	215.00	1	0	34
266.00	266.00	1	0	34
277.00	298.00	8	2	36
303.00	327.00	25	7	43
333.00	363.00	17	5	48
370.00	370.00	1	0	48
413.00	431.00	3	1	49
438.00	465.00	16	5	54
472.00	495.00	20	6	60
504.00	714.00	61	17	77
727.00	927.00	37	11	87
953.00	1144.00	17	5	92
1177.00	1315.00	8	2	95
1388.00	1512.00	5	1	96
1590.00	1790.00	10	3	99
1854.00	1918.00	2	1	99
0.0	0.0			
0.0	0.0			
2559.00	2559.00	1	0	100
0.0	0.0			
0.0	0.0			
0.0	0.0			
0.0	0.0			
3746.00	3746.00	1	0	100

MISSING DATA 128.

GOOD N 351.

MEANS 499.4756

VARIANCES 205844.8750

S.D. 453.7014

DESCRIPTIVE STATS PROGRAM

VARIABLE 20, DENTS11,

FROM DATA FILE

B

ALL

LOW	HIGH	N	PCT	CUM
0.0	0.0	41	11	11
0.0	0.0			
0.0	0.0			
0.0	0.0			
160.00	186.00	56	15	27
190.00	219.00	22	6	33
235.00	240.00	2	1	33
0.0	0.0			
317.00	333.00	10	3	36
339.00	370.00	27	7	43
377.00	408.00	15	4	47
416.00	451.00	7	2	49
454.00	472.00	3	1	50
495.00	521.00	14	4	54
531.00	560.00	17	5	58
571.00	702.00	38	10	69
714.00	840.00	30	8	77
851.00	971.00	25	7	84
1010.00	1133.00	11	3	87
1139.00	1262.00	17	5	92
1286.00	1388.00	7	2	93
1431.00	1541.00	11	3	96
1568.00	1670.00	5	1	98
1706.00	1782.00	3	1	99
0.0	0.0			
2025.00	2025.00	1	0	99
2186.00	2190.00	2	1	99
2326.00	2326.00	1	0	100
0.0	0.0			
2696.00	2696.00	1	0	100

MISSING DATA 113.

GOODD N 366.

MEANS 564.9971

VARIANCES 219679.0625

S.D. 468.6992

Appendix III

Correlation matrix for 28 variables in the study.
See table 7.3 for variable descriptions.

DESCRIPTIVE STATS PROGRAM

INTER OF 8

***PAGE 1 OF FILE BIN

POSITION	1	2	3	4	5	6	7	8
LABEL	MAT.AGE	NO.CONCP	CONSANG.	GEST.AGE	SEX	MATS.PER	FOOD.PER	NO.STLB
1 MAT.AGE	1.00000	0.67545	-0.05412	-0.01369	0.02635	-0.00548	-0.05775	0.20731
2 NO.CONCP	0.67545	1.00000	0.09080	0.01558	0.04851	-0.07715	-0.09489	0.43848
3 CONSANG.	-0.05412	0.09080	1.00000	0.08281	0.04416	-0.08159	-0.03469	0.09177
4 GEST.AGE	-0.01369	0.01558	0.08281	1.00000	0.05894	0.01278	-0.08796	0.05717
5 SEX	0.02635	0.04851	0.04416	0.05894	1.00000	-0.02651	-0.04349	0.08477
6 MATS.PER	-0.00548	-0.07715	-0.08159	0.01278	-0.02651	1.00000	0.27976	0.04575
7 FOOD.PER	-0.05775	-0.09489	-0.03469	-0.08796	-0.04349	0.27976	1.00000	-0.02039
8 NO.STLB	0.20731	0.43848	0.09177	0.05717	0.08477	0.04575	-0.02039	1.00000
9 BIRTH.WT	-0.04370	0.06903	-0.01727	0.28877	-0.03192	0.01562	-0.06926	-0.01972
10 DENTS01	-0.04403	-0.09760	-0.00982	0.11637	0.00933	0.06801	0.03825	0.00351
11 DENTS02	0.02105	-0.00421	-0.03332	-0.10543	-0.12163	0.14262	0.11828	0.01373
12 DENTS03	0.06016	0.02538	0.02661	0.04569	-0.00155	0.03497	-0.05530	-0.01204
13 DENTS04	-0.06159	-0.07532	-0.01797	-0.01554	-0.07635	-0.02422	0.03303	0.01258
14 DENTS05	-0.11653	-0.10805	0.10937	-0.03030	-0.07136	-0.05986	-0.10696	0.00508
15 DENTS06	-0.10526	-0.12155	-0.03161	0.06870	-0.22666	0.04741	0.03466	-0.09584
16 DENTS07	-0.03273	-0.04663	-0.11924	0.05107	0.00013	-0.00725	0.01852	-0.09983
17 DENTS08	0.00413	-0.01091	0.01048	-0.00310	-0.25502	0.11380	-0.02751	-0.10269
18 DENTS09	0.04555	0.00869	-0.05650	-0.01812	-0.04564	-0.04287	0.05842	0.06778
19 DENTS10	-0.02999	-0.05128	0.00532	-0.07186	-0.07534	0.00492	0.11306	-0.04883
20 DENTS11	0.02675	0.02871	-0.01536	0.05397	-0.06438	-0.03928	-0.09230	-0.00874
21 DENTS12	-0.01568	-0.02808	-0.03019	-0.02787	-0.03410	0.02093	0.10586	-0.05265
22 AGE	-0.04242	-0.03599	0.05185	0.03917	-0.15025	-0.04419	-0.06067	-0.10220
23 NO.PER.T	-0.02029	-0.01049	0.05857	0.02505	0.07223	-0.00331	-0.01961	-0.03984
24 DMF	-0.03176	0.01130	0.05535	-0.03411	0.08934	0.05799	-0.02945	-0.01442
25 BED.2.WK	0.03197	-0.01544	0.01211	-0.09218	-0.06952	0.02846	0.03786	0.07163
26 CONVULNS	-0.05040	-0.06406	0.04481	0.03844	-0.03803	-0.02197	-0.04412	0.02436
27 NO.PRT.T	0.01542	0.01244	-0.06902	-0.00348	-0.05590	-0.03522	-0.02952	0.02235
28 DEF	-0.01444	0.00455	0.00361	-0.05330	-0.01065	-0.03480	-0.00532	0.07610

DESCRIPTIVE STATS PROGRAM

INTERS OF 8

***PAGE 2 OF FILE BIN

POSITION	9	10	11	12	13	14	15	16
LABEL	BIRTH.WT	DENTS01	DENTS02	DENTS03	DENTS04	DENTS05	DENTS06	DENTS07
1 MAT.AGE	-0.04370	-0.04403	0.02105	0.06016	-0.06159	-0.11653	-0.10526	-0.03273
2 NO.CONCP	0.06903	-0.09760	-0.00421	0.02538	-0.07532	-0.10805	-0.12155	-0.04663
3 CONSANG.	-0.01727	-0.00982	-0.03332	0.02661	-0.01797	0.10937	-0.03161	-0.11924
4 GEST.AGE	0.28877	0.11637	-0.10543	0.04569	-0.01554	-0.03030	0.06870	0.05107
5 SEX	-0.03192	0.00933	-0.12163	-0.00155	-0.07635	-0.07136	-0.22666	0.00013
6 MATS.PER	0.01562	0.06801	0.14262	0.03497	-0.02422	-0.05986	0.04741	-0.00725
7 FOOD.PER	-0.06926	0.03825	0.11828	-0.05530	0.03303	-0.10696	0.03466	0.01852
8 NO.STLB	-0.01972	0.00351	0.01373	-0.01204	0.01258	0.00508	-0.09584	-0.09983
9 BIRTH.WT	1.00000	0.07216	0.00569	0.04545	0.10287	-0.06715	0.09899	-0.02394
10 DENTS01	0.07216	1.00000	-0.13012	0.03058	-0.13033	0.06056	0.00561	-0.07763
11 DENTS02	0.00569	-0.13012	1.00000	-0.16681	0.47066	0.00959	0.29407	0.05377
12 DENTS03	0.04545	0.03058	-0.16681	1.00000	0.08560	0.09291	0.04602	-0.06940
13 DENTS04	0.10287	-0.13033	0.47066	0.08560	1.00000	0.08010	0.36269	0.00310
14 DENTS05	-0.06715	0.06056	0.00959	0.09291	0.08010	1.00000	0.08398	-0.06366
15 DENTS06	0.09899	0.00561	0.29407	0.04602	0.36269	0.08398	1.00000	-0.01484
16 DENTS07	-0.02394	-0.07763	0.05377	-0.06940	0.00310	-0.06366	-0.01484	1.00000
17 DENTS08	0.07110	0.03472	0.19125	-0.01662	0.29654	0.03847	0.64439	0.02906
18 DENTS09	-0.05993	0.06577	-0.15518	-0.04425	0.01820	-0.07732	0.08310	0.01525
19 DENTS10	0.07558	-0.06787	0.32135	-0.00838	0.39247	-0.06863	0.39222	-0.04441
20 DENTS11	0.08051	0.11126	-0.05080	-0.02722	0.05797	0.05868	0.04767	0.07768
21 DENTS12	0.03982	-0.07938	0.18527	0.00738	0.36954	0.00004	0.28017	-0.10867
22 AGE	-0.03713	0.06465	0.00773	-0.05481	-0.14550	0.03195	0.23920	0.05116
23 NO.PFR.T	-0.00522	-0.02269	0.17324	-0.09347	-0.10717	0.03706	0.14444	0.01654
24 DMF	-0.02881	-0.05361	0.14027	-0.04904	0.01002	0.01794	0.12710	-0.02748
25 BED.2.WK	0.00344	-0.06194	0.06745	-0.05404	-0.02171	-0.06445	0.05679	0.04570
26 CONVULNS	0.00496	-0.03528	-0.03369	0.01860	-0.00691	-0.03206	0.01998	0.02744
27 NO.PRI.T	0.00486	-0.00106	-0.24323	0.08238	0.06677	0.01055	-0.16220	-0.01352
28 DEF	-0.01032	-0.10284	0.04635	0.04622	0.09966	0.04235	0.06063	0.01016

DESCRIPTIVE STATS PROGRAM

INTERS OF R

***PAGE 3 OF FILE BIN

POSITION	17	18	19	20	21	22	23	24
LABEL	DENTS08	DENTS09	DENTS10	DENTS11	DENTS12	AGE	NO.PER.T	DMF
1 MAT.AGE	0.00413	0.04555	-0.02999	0.02675	-0.01568	-0.04242	-0.02029	-0.03176
2 NO.CONCP	-0.01091	0.00869	-0.05128	0.02871	-0.02808	-0.03599	-0.01049	0.01130
3 CONSANG.	0.01048	-0.05650	0.00532	-0.01536	-0.03019	0.05185	0.05857	0.05535
4 GEST.AGE	-0.00310	-0.01812	-0.07186	0.05397	-0.02787	0.03917	0.02505	-0.03411
5 SEX	-0.25502	-0.04564	-0.07534	-0.06438	-0.03410	-0.15025	0.07223	0.08934
6 MATS.PER	0.11380	-0.04287	0.00492	-0.03928	0.02093	-0.04419	-0.00331	0.05799
7 FOOD.PER	-0.02751	0.05842	0.11306	-0.09230	0.10586	-0.06067	-0.01961	-0.02945
8 NO.STLB	-0.10269	0.06778	-0.04883	-0.00874	-0.05265	-0.10220	-0.03984	-0.01442
9 BIRTH.WT	0.07110	-0.05993	0.07558	0.08051	0.03982	-0.03713	-0.00522	-0.02881
10 DENTS01	0.03472	0.06577	-0.06787	0.11126	-0.07938	0.06465	-0.02269	-0.05361
11 DENTS02	0.19125	-0.15518	0.32135	-0.05080	0.18527	0.00773	0.17324	0.14027
12 DENTS03	-0.01662	-0.04425	-0.00838	-0.02722	0.00738	-0.05481	-0.09347	-0.04904
13 DENTS04	0.29654	0.01820	0.39247	0.05797	0.36954	-0.14550	-0.10717	0.01002
14 DENTS05	0.03847	-0.07732	-0.06863	0.05868	0.00004	0.03195	0.03706	0.01794
15 DENTS06	0.64439	0.08310	0.39222	0.04767	0.28017	0.23920	0.14444	0.12710
16 DENTS07	0.02906	0.01525	-0.04441	0.07768	-0.10867	0.05116	0.01654	-0.02748
17 DENTS08	1.00000	0.08276	0.21488	-0.01984	0.31732	0.26207	0.18396	0.15462
18 DENTS09	0.08276	1.00000	-0.11270	0.09356	-0.03943	0.02951	0.02052	0.03996
19 DENTS10	0.21488	-0.11270	1.00000	-0.11257	0.67474	-0.11950	-0.11425	-0.01427
20 DENTS11	-0.01984	0.09356	-0.11257	1.00000	-0.12672	0.18568	0.15028	-0.02265
21 DENTS12	0.31732	-0.03943	0.67474	-0.12672	1.00000	-0.19745	-0.16811	0.02367
22 AGE	0.26207	0.02951	-0.11950	0.18568	-0.19745	1.00000	0.75102	0.19590
23 NO.PER.T	0.18396	0.02052	-0.11425	0.15028	-0.16811	0.75102	1.00000	0.30880
24 DMF	0.15462	0.03996	-0.01427	-0.02265	0.02367	0.19590	0.30880	1.00000
25 BED.2.WK	0.07986	0.05630	-0.00148	0.04399	-0.04121	0.05658	0.06415	0.06683
26 CONVULNS	-0.04623	-0.06718	0.08515	-0.04042	-0.02418	-0.07922	-0.06980	-0.07081
27 NO.PRI.T	-0.16985	-0.02071	0.03947	-0.16777	0.12268	-0.70569	-0.91611	-0.31310
28 DEF	-0.05383	-0.01957	0.12165	-0.14609	0.16847	-0.57131	-0.58321	0.06862

DESCRIPTIVE STATS PROGRAM

INTER 8

***PAGE 4 OF FILE BIN

POSITION	25	26	27	28
LABEL	BED.2.WK	CONVULNS	NO.PRI.T	DEF
1 MAT.AGE	0.03197	-0.05040	0.01542	-0.01444
2 NO.CONCP	-0.01544	-0.06406	0.01244	0.00455
3 CONSANG.	0.01211	0.04481	-0.06902	0.00361
4 GEST.AGE	-0.09218	0.03844	-0.00348	-0.05330
5 SFX	-0.06952	-0.03803	-0.05590	-0.01065
6 MATS.PER	0.02846	-0.02197	-0.03522	-0.03480
7 FOOD.PER	0.03786	-0.04412	-0.02952	-0.00532
8 NO.STLB	0.07163	0.02436	0.02235	0.07610
9 BIRTH.WT	0.00344	0.00496	0.00486	-0.01032
10 DENTS01	-0.06194	-0.03528	-0.00106	-0.10284
11 DENTS02	0.06745	-0.03369	-0.24323	0.04635
12 DENTS03	-0.05404	0.01860	0.08238	0.04622
13 DENTS04	-0.02171	-0.00691	0.06677	0.09966
14 DENTS05	-0.06445	-0.03206	0.01055	0.04235
15 DENTS06	0.05679	0.01998	-0.16220	0.06063
16 DENTS07	0.04570	0.02744	-0.01352	0.01016
17 DENTS08	0.07986	-0.04623	-0.16985	-0.05383
18 DENTS09	0.05630	-0.06718	-0.02071	-0.01957
19 DENTS10	-0.00148	0.08515	0.03947	0.12165
20 DENTS11	0.04399	-0.04042	-0.16777	-0.14609
21 DENTS12	-0.04121	-0.02418	0.12268	0.16847
22 AGE	0.05658	-0.07922	-0.70569	-0.57131
23 NO.PER.T	0.06415	-0.06980	-0.91611	-0.58321
24 DMF	0.06683	-0.07081	-0.31310	0.06862
25 BED.2.WK	1.00000	0.03967	-0.08914	-0.04007
26 CONVULNS	0.03967	1.00000	0.09967	0.09146
27 NO.PRI.T	-0.08914	0.09967	1.00000	0.62889
28 DEF	-0.04007	0.09146	0.62889	1.00000

ENDS

NUMBER OF ERRORS DURING THIS RUN WAS 0

Appendix IV

Cross-tabulation by levels of birth weight and gestational age. Analysis of variance of means for variables specified. Only variables with row, column or interaction affects significant at the 5% level are included.

DESCRIPTIVE STATS PROGRAM

INPUT IS

B

MEANS ARE OF VARIABLE NUMBER 3, LABEL IS CONSANG.

ROW VARIABLE IS NUMBER 4, LABEL IS GEST.AGE

COLUMN VARIABLE IS NUMBER 9, LABEL IS BIRTH.WT

N MATRIX OF CASES WITH NON-MISSING DATA ON ALL 3 VARIABLES.

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	62.	54.	19.	13.	10.	158.
2-2	18.	46.	23.	20.	14.	121.
3-4	22.	64.	48.	42.	24.	200.
SUM	102.	164.	90.	75.	48.	479.

 CHI SQUARE = 56.22
 WORST EXPECTED VALUE = 12.1
 D.F. = 8.

 MEANS OF VARIABLE CONSANG.

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	0.01	0.02	0.01	0.01	0.02	0.01
2-2	0.01	0.02	0.02	0.01	0.01	0.01
3-4	0.02	0.02	0.02	0.02	0.03	0.02
SUM	0.02	0.02	0.02	0.01	0.02	0.02

 SUMMARY OF ANALYSIS OF VARIANCE
 SOURCE S.S. D.F. MEAN SQ F

ROW	0.01	2.	0.00	4.23
COL	0.00	4.	0.00	0.51
R.BY.C	0.00	8.	0.00	0.67
WITHIN CELL	0.30	464.	0.00	

DESCRIPTIVE STATS PROGRAM

INPUT IS

B

MEANS ARE OF VARIABLE NUMBER 7, LABEL IS FOOD.PER

ROW VARIABLE IS NUMBER 4, LABEL IS GEST.AGE

COLUMN VARIABLE IS NUMBER 9, LABEL IS BIRTH.WT

N MATRIX OF CASES WITH NON-MISSING DATA ON ALL 3 VARIABLES.

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	62.	54.	19.	13.	10.	158.
2-2	18.	46.	23.	20.	14.	121.
3-4	22.	64.	48.	42.	24.	200.
SUM	102.	164.	90.	75.	48.	479.

 CHI SQUARE = 56.22
 WORST EXPECTED VALUE = 12.1
 D.F. = 8.

 MEANS OF VARIABLE FOOD.PER

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	3.07	2.99	2.59	3.42	3.54	3.04
2-2	3.51	3.08	3.11	3.08	2.30	3.06
3-4	2.93	2.78	2.83	2.81	2.91	2.83
SUM	3.12	2.93	2.85	2.99	2.86	2.96

 SUMMARY OF ANALYSIS OF VARIANCE
 S.S. D.F. MEAN SQ F

ROW	4.20	2.	2.10	2.00
COL	5.02	4.	1.26	1.19
R.BY.C	26.15	8.	3.27	3.11
WITHIN CELL	488.27	464.	1.05	

DESCRIPTIVE STATS PROGRAM

INPUT IS B

MEANS ARE OF VARIABLE NUMBER 13, LABEL IS DENTS04

ROW VARIABLE IS NUMBER 4, LABEL IS GEST.AGE

COLUMN VARIABLE IS NUMBER 9, LABEL IS BIRTH.WT

N MATRIX OF CASES WITH NON-MISSING DATA ON ALL 3 VARIABLES.

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	46.	35.	15.	8.	6.	110.
2-2	18.	31.	14.	14.	8.	85.
3-4	17.	43.	29.	31.	18.	138.
SUM	81.	109.	58.	53.	32.	333.

```

*****
CHI SQUARE = 37.40
WDRST EXPECTED VALUE = 8.2
D.F. = 8.
*****
MEANS OF VARIABLE DENTS04
*****

```

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	59.91	61.09	61.57	61.46	62.92	60.79
2-2	62.80	59.42	61.01	60.94	62.77	60.97
3-4	62.16	60.12	60.55	60.74	62.68	60.93
SUM	61.02	60.23	60.92	60.90	62.75	60.89

```

*****
SUMMARY OF ANALYSIS OF VARIANCE
SOURCE      S.S.      D.F.      MEAN SQ      F
ROW          0.97        2.        0.48        0.03
COL        168.82        4.       42.21        2.66
R.BY.C      105.25        8.       13.16        0.83
WITHIN CELL 5042.00     318.      15.86

```

DESCRIPTIVE STATS PROGRAM

INPUT IS

B

MEANS ARE OF VARIABLE NUMBER 24, LABEL IS DMF

ROW VARIABLE IS NUMBER 4, LABEL IS GEST.AGE
COLUMN VARIABLE IS NUMBER 9, LABEL IS BIRTH.WT

N MATRIX OF CASES WITH NON-MISSING DATA ON ALL 3 VARIABLES.

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	62.	54.	19.	13.	10.	158.
2-2	18.	46.	23.	20.	14.	121.
3-4	22.	64.	48.	42.	24.	200.
SUM	102.	164.	90.	75.	48.	479.

CHI SQUARE = 56.22
WORST EXPECTED VALUF = 12.1
D.F. = 8.

MEANS OF VARIABLE DMF

GEST.AGE GOES DOWN BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	1.08	1.09	1.42	1.00	0.70	1.09
2-2	1.39	1.57	0.87	0.40	0.79	1.12
3-4	1.05	0.92	0.94	0.93	1.67	1.03
SUM	1.13	1.16	1.02	0.80	1.21	1.08

SUMMARY OF ANALYSIS OF VARIANCE
SOURCE S.S. D.F. MEAN SQ F
ROW 0.56 2. 0.28 0.17
COL 7.63 4. 1.91 1.15
R.BY.C 28.39 8. 3.55 2.14
WITHIN CELL 769.71 464. 1.66

DESCRIPTIVE STATS PROGRAM

INPUT IS

B

MEANS ARE OF VARIABLE NUMBER 25, LABEL IS BED.2.WK

ROW VARIABLE IS NUMBER 4, LABEL IS GEST.AGE

COLUMN VARIABLE IS NUMBER 9, LABEL IS BIRTH.WT

N MATRIX OF CASES WITH NON-MISSING DATA ON ALL 3 VARIABLES.

GEST.AGE GOES DOWN

BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	62.	54.	19.	13.	10.	158.
2-2	18.	46.	23.	20.	14.	121.
3-4	22.	64.	48.	42.	24.	200.
SUM	102.	164.	90.	75.	48.	479.

```

*****
CHI SQUARE = 56.22
WORST EXPECTED VALUE = 12.1
D.F. = 8.
*****
MEANS OF VARIABLE BED.2.WK
*****

```

GEST.AGE GOES DOWN

BIRTH.WT GOES ACROSS.

	0-1	2-2	3-3	4-4	5-5	
0-1	0.24	0.46	0.32	0.38	0.70	0.37
2-2	0.22	0.30	0.26	0.25	0.29	0.27
3-4	0.32	0.22	0.23	0.33	0.08	0.24
SUM	0.25	0.32	0.26	0.32	0.27	0.29

```

*****
SUMMARY OF ANALYSIS OF VARIANCE
SOURCE      S.S.      D.F.      MEAN SQ      F
ROW          2.27        2.        1.13        3.00
COL          0.47        4.        0.12        0.31
R.BY.C       3.39        8.        0.42        1.12
WITHIN CELL 175.33      464.      0.38

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