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ADMINISTRATIVE BACKGROUND

As is a matter of common knowledge, in 1960 the International Council of Scientific Unions (ICSU) took the initiative in the promulgation of an International Biological Program. As originally envisioned by ICSU, the objectives of this program were the world-wide study of

(1) organic production on the land, in fresh waters, and in the seas, and the potentialities and uses of new as well as existing natural resources, and

(2) human adaptability to changing conditions.

A Planning Committee appointed by ICSU in turn established a number of subcommittees to consider various aspects of the program and to elaborate a more extended protocol. These various subcommittees combined their efforts into a series of suggestions and recommendations which the Planning Committee coordinated and submitted to ICSU in November of 1963. ICSU, after approving these suggestions and recommendations, then called upon the various countries having representation in ICSU through national societies to formulate national programs. The time table for IBP, several times revised, consists of a "planning phase," which officially terminated in mid-1967, and an "operational phase," to continue until mid-1972.

It has been clearly understood from the outset that the various national committees were in no way bound by this international formulation, it being designed to provide convenient guidelines. Thus far 10 countries in North, Central, and South America have established committees to formulate national programs, and four other countries may do so soon. It will be the purpose of this presentation to attempt to point out the manner in which a variety of types of studies of the American Indian fall within the framework of the IBP, and especially that section concerned with human adaptability. In fact, the Indian provides the Americas with a unique resource in IBP-oriented studies and at the same time presents interdigitating medical and humane challenges which are worthy of the consideration of this Organization.

At all of the various levels of consideration of human adaptability, it has been clear there are two interrelated components, the genetic, which sets the limit of the organism's ability to respond, and the physiological, which determines the range of response available to the organism, given its genetic set. At one extreme in the spectrum of interests that can be brought to bear on human adaptability there is environmental physiology, at the other extreme population genetics--and in between there is room for many aspects of modern medicine and anthropology.

From the earliest considerations of most of the various committees and subcommittees concerned with Human Adaptability, it has been apparent that the surviving primitive populations represent an opportunity to study physiological and genetic adaptations potentially quite different from those of highly civilized groups. Parenthetically, although our cultural orientation is such that we tend to view many of these surviving primitive groups as representing extremes of adaptability, the fact is that they have lived under their conditions far longer than we under ours. Viewed from their vantage point, we are the ones pressing for new limits of adaptability, with it only an article of faith that we will adapt to our man-made environment as successfully as they to theirs. We must note in passing that some of the adaptations of these groups are complex and ingenious, and that the term "primitive" as commonly used is something of a misnomer, equating to "non-literate with a relatively simple technology."

In late 1962 the World Health Organization convened a Scientific Group on Research in Population Genetics of Primitive Groups, whose purpose was to consider studies of populations of unusual genetic interest, with particular reference to the surviving hunting and food-gathering groups of the world, to advise on the most suitable populations for such studies, and to draw up appropriate research designs. The pertinence of this to IBP-related developments is obvious. In the preliminary inventory of these societies published in the report of the Scientific Group, various South American tribes figure prominently (26). This report, incidentally, was updated in the summer of 1967 and a revised version will be issued shortly.

A recurrent consideration in the consultations of both IBP-related and WHO-related groups has been the rate at which these primitive groups are disappearing. It can without exaggeration be said that ours is probably the last generation to be privileged to study such groups in a relatively pristine state. If there are important scientific lessons to be learned--and the WHO document would seem to develop that case adequately--then there is an urgency to this problem not shared by many other areas of research.

THE DIMENSIONS OF INDIAN-ORIENTED STUDIES

These are days in which those of us concerned with human biology see our species as beset by a growing number of pressing problems of our own making:

the population increase, trace chemicals in food stuffs, air pollution, water pollution, the so-called stress diseases, cultural alienation, to mention only a few. Each of these problems has reached a magnitude such that concerted action on a scale foreign to our past actions is called for. But I submit that behind these immediate problems lurks a far larger issue. Now that man so largely controls both the environment and his reproduction, is there any more important long-range objective than that we understand the genetic potentialities of the individual and the species, the manner in which this potential interacts with an environment which is increasingly man-made, and the rate of genetic change in response to a changing environment. You will recognize that I have only restated in a different context the need to understand the genetic aspects of human adaptability. The American Indian offers prime research material for this objective. The principal lines of attack can be conveniently summarized under three headings (cf. 12).

1. Population structure and natural selection in primitive man. - One of the basic tenets of biology is of course a belief in the role of natural selection in shaping each species to its ecological niche. As biologists we believe that natural selection has guided human evolution, and will continue to guide the evolution necessary for a successful genetic adjustment to a changing world. It is clear that modern man evolved under circumstances approximating the conditions found in primitive cultures. Otherwise stated, there is no evidence that the developments of the past few thousand years have yet resulted in any very significant modifications of man's genetic potential. It follows that

one way of understanding the genetic impact of our changing environment is from the baseline supplied by detailed knowledge of primitive man in his primitive ecosystem. The simple fact is that at present we know virtually nothing about how selection works in man. What few insights we have are largely based on the results of artificial selection with experimental animals, and deal with traits, such as extremes of egg production or milk yield, considerably more important to us than to the animal species involved.

What the geneticist terms "population structure" places limits on the effectiveness of natural or artificial selection. Thus, hand in hand with efforts to understand selective pressures must go efforts to understand the genetic structure of populations. To the geneticist, this means patterns of mating, fertility and survival; amount of inbreeding; migrational patterns; mutation rates; and so on. Although some data on these subjects are to be found in the voluminous anthropological literature, in the main it simply lacks the precision and depth necessary to the precise statistical treatments of the geneticist.

Even with all the facilities of modern science and the conveniences of our culture, such comprehensive studies remain extremely difficult in civilized countries. How much more difficult are they, then, in the remote primitive populations, problems of logistics and communication being what they are. Even so, based on our own experience of the past several years and that of several other groups with kindred interests, it is clear a variety of types of data relevant to population structure can be collected.

In 1962, aided by a grant from this Organization, Dr. Francisco Salzano of the Universidade do Rio Grande do Sul, Brazil, and I, with several collaborators, undertook a pilot study on the Xavante of the Brazilian Mato Grosso (13). These and further studies on the Xavante, in 1963 and 1964, raised a number of rather basic questions for population genetics (14), but it was felt that the Xavante were neither a large enough group, nor sufficiently undisturbed, for a critical approach to these questions. Accordingly, after a careful consideration of the possibilities, a second study was undertaken, concerned with the Yanomama Indians of Venezuela and Brazil, and involving as principal colleagues, in addition to Dr. Salzano, also Dr. Miguel Layrisse and Dr. Tulio Arends of the Instituto Venezolano de Investigaciones Cientificas of Venezuela, and Dr. W. J. Schull and Dr. Napoleon Chagnon of the University of Michigan. We have now been in the field on three different occasions. The composition of the team varies from year to year, but ideally includes an ethnologist, linguist, physical anthropologist, geneticist, and several physicians. Although the precise nature of the data collected depends upon local circumstances, under optimal conditions we assemble as complete demographic and genealogical data as possible, conduct physical, dental, and anthropological examinations, and obtain blood, urine, saliva and stool specimens for a variety of genetic and other determinations. The effort to understand better man's interaction with his environment carries far beyond the identification of genetic traits--we are fortunate to have the collaboration of such groups as the Communicable Disease Center of the U. S. Public Health Service, the Virus Institute at I.V.I.C., and many specialized laboratories at the University of Michigan.

This is not the time for a detailed review of the findings on either the Xavante or Yanomama, which in any event must be regarded as preliminary.

Not at all surprisingly, both the population structure of, and biological pressures on, these people are qualitatively and quantitatively different from those of civilized groups. These are populations in which infertility is rare, practically all women contributing to the next generation; in which effective fertility seems intermediate; infant and childhood mortality also intermediate; and in which the variance of male reproductive indices is significantly greater than of female (15). A surprising amount of genetic microdifferentiation between villages has been encountered (1), originating, we believe, in the fission-fusion pattern which dominates village proliferation, and which results when a new village comes into being in a very non-random sampling of the tribal gene pool. We reason from this that if new tribes originate in general as do new villages, then chance may have played a greater role in much measurable human genetic variation than heretofore seemed likely. The roles of traumatic, infectious, and nutritional disease in determining survival are far different than in the next stage on the cultural ladder, namely, in relatively densely populated agricultural societies.

We do not pretend as yet to understand the full genetic implications of all that we see. One reason for our lack of understanding is that a substantial portion of the mathematical theory of population genetics is currently being reworked. A second reason is that the data have a complexity such that precise mathematical formulations do not appear imminent, and we are being forced to involved computer simulation programs to explore the genetic consequences of the differences between these societies and our own. However, even at this state it is very clear that it will be possible to define objectives and test hypotheses in a way that will justify the effort expended.

I mentioned above that a substantial portion of the mathematical theory of population genetics is being reworked. One of the most provocative developments in the biomedicine of the past 20 years has been the realization of the extent of man's concealed genetic variability, as revealed by modern biochemical techniques. Many of the newly recognized variant types occur in populations in such frequencies that we speak of the underlying systems as genetic polymorphisms. The maintenance of such polymorphisms is thought to require selective pressures of one kind or another, but not only is the nature of these forces unknown, in addition under the previous formulations the mortality and fertility structure of our population scarcely seems adequate to accommodate the necessary selection, and new formulations are being considered (7, 9, 25). Understanding how all this variability is maintained is one of the great challenges to the human biologist (cf. 8, 16). Now, the genetic polymorphisms are well represented in all the primitive populations studied to date. This is where they came into being. Accordingly, it seems self evident that despite the inherent difficulties, we must make every effort to conduct studies in depth of population structure and the relationship at this cultural level between the polymorphisms and specific biological attributes.

There is an urgent scientific need, while the opportunity exists, for similar studies on as many as possible of the other unacculturated groups of Indians, None of the surviving primitive Indian communities can safely be labelled "typical"--each may be unusual in one or several respects. Only from the perspective of numerous studies in depth can we begin with any assurance to factor out the significant common denominators that have guided human evolution. Already parallel studies are in progress on such groups as the Cayapo of Brazil by Salzano and colleagues and the Kashinawa of Peru and Brazil by Johnston and colleagues, as well as in other parts of the world, and more are to be hoped for.

2. The rate of human evolution, i.e., genetic diversification. - Despite the many unanswered questions discussed earlier in this Symposium by Professors Griffin, Cruxent, and Laughlin, the date and place of arrival of the Indian in the Americas is more accurately known than the corresponding information for any other major subdivision of mankind. In view of what can be deduced concerning population density in northern Europe 20,000 years ago, we may surmise that the total number of immigrants across the Bering Bridge, whether they came in one or several discrete waves, was not large. The genetic characteristics of this original group will of course forever be conjectural, but let us assume that the tribal population(s) concerned had the range of variability we see in such a group as the Yanomama. (I am assuming in this discussion that the contribution to the gene pool of individuals reaching the Americas other than by the Bering Bridge is negligible.) Once here, extension throughout the Americas seems to have been rapid. In this extension, the diversity of habitats which was explored and occupied represents almost the extremes of the habitable portions of the earth. If we make the assumption of a reasonably homogeneous beginning, then the diversity of types of Indians at the time of the rediscovery of this continent 5 centuries ago represents an unusual opportunity to measure the rate of human evolution.

Much of the early thinking on this topic drew on morphological characteristics, and these, as Professor Comas has just demonstrated, still remain valid and pertinent. However, in recent years the newly discovered polymorphisms mentioned earlier have provided a powerful battery of objective indicators of genetic distance. Dr. Layrisse has just provided us with an overview of how great the range is with regard to a variety of specific systems. In theory, for any given genetic system the position of each Indian population with respect to all the others can be defined by a point in a space which has one less dimension than there are alleles in the system, the precise position in this space being determined by the frequency of each allele. Further in theory, when one considers many different genetic systems simultaneously, the position of each population vis-a-vis the others can be plotted in a **space** which now has as many dimensions as there are genetic systems. Previously, the computations when a considerable number of systems were involved were as laborious as the above description sounds (6, 22). But the advent of the modern computers has dramatically altered the situation, and now a number of groups are developing computer-based measurements of population distance (cf. 3).

Although considerable progress has been made, there is still a great deal to be done in the way of characterizing the genetic attributes of the relatively pure Indian groups, as a basis for exploring the evolutionary problem discussed above. Incidentally, the HA/IBP/IUBS emphasized the need for continuing efforts at the genetic characterization of all the human strains, so that this type of investigation of the Indian readily fits into a larger framework. The published data on the Indian are widely scattered, no survey having been attempted since those of Mourant (10, 11) and Salzano (18). Dr. Richard Post and I have now completed a compilation of all publications prior to November, 1967, which deal with the principal genetic polymorphisms known to occur in the Indian. The rate of discovery of new polymorphisms being what is is, any such compilation is soon dated, but for the specialist it at least provides a nidus for updating. The 271 papers on which the tabulations are based attest to the strong interest in this subject. Since the data on unmixed Indian groups have in most contexts far greater interest than the data on mixed, an effort has been made in the tabulation to recognize three levels of miscegenation, namely, 1) essentially none, 2) known, but probably accounting for less than 5 per cent of the gene pool, and 3) greater than 5 per cent. It is our expectation that the tabulation, accompanied by the necessary bibliography, will be published as an appendix to the Proceedings of this Symposium. The tabulation includes data on the following polymorphic systems: ABO, Rh, MN, Kidd, Duffy, Diego, P. Lewis, haptoglobins, transferrins, and Gm, these being the polymorphic systems on which there seemed enough data to warrant a tabulation. Gene frequencies have been computed for each study with computer programs written in Fortran and available on request.

In closing this section, let me agree with those who feel there has already been quite enough of surveying populations for gene frequencies in the vague hope that someday the information will be valuable (cf. 2). In the case of the Indian, however, such surveys bear on a clearly defined problem on which considerable progress may be expected in the near future.

3. <u>The response of genetic systems to a rapidly changing environment</u>. - As mentioned earlier, we recognize that our species is all over the world subjected to a rapidly changing environment. Unfortunately, only in the last few years have biology and medicine found themselves in a position to begin to document with any precision what biological adjustments really take place. We have probably lost forever the opportunity to study what transpired in Caucasian populations. We are about to lose the opportunity to document what happens in Negro or Mongoloid (including Indian) populations.

The transition of surviving primitive Negro or Indian groups will be telescoped into a far shorter time period than was true for Caucasian groups. Thus, some Indian groups will be called upon to move from the Stone Age to the Atomic Age in a few hundred years, whereas the transition for most Caucasian groups took thousands. It seems a tenable hypothesis that here is an opportunity to study changes in population structure and adjustments to new stresses which we must not lose.

As for the previous two sections, so here the intellectual challenge is to convert an easily enunciated but somewhat diffuse series of problems into specific issues susceptible to precise study. A number of exact studies of population structure in transitional groups have already been completed or are in progress, notably, those of Salzano and colleagues on the Caingang of Brazil (19, 20), of Layrisse and colleagues on the Warao of Venezuela, of Covarrubias and colleagues on the Pewenche of Chile, and of Cann and colleagues on certain Quiche speakers of Guatamala. There are also studies within the United States on groups in a more advanced stage of the transition, namely by Spuhler and colleagues (21) on the Navaho and Hackenberg (5) on the Papago.

There are also in progress studies of specific medical issues which arise in transitional groups, as the latter portion of this Symposium will attest. The work of Roche and colleagues, to be described later in this Symposium, in particular will illustrate just how rapid and subtle may be the changes introduced by minimal acculturation. If genetic factors are important in the susceptibility to the thyroid hyperplasia and diabetes mellitus now so common in certain Indian groups, then, because of the recency, frequency, and intensity of the phenomena, these groups may be unusually favorable material for the study of these genetic factors.

Some unpublished studies of Drs. Warren Eveland, William Oliver, and myself may help point to some of the nuances of this transition. Six *E. coli* strains were isolated by Dr. Eveland from each of 77 Yanomama stools, each stool from a different subject. An effort is in progress to type each of the resulting 462 strains, utilizing some 140 different typing sera. Thus far approximately 44 per cent of the strains fail to type out. By contrast, experience indicates only a very small fraction of *E. coli* strains isolated in the United States would fail to type. What remains to be determined is whether this is a unique finding in a long isolated population, or whether similar studies on other such groups will reveal the same pattern, with the inference of a predictable shift in the intestinal flora with acculturation.

SOME MORAL ISSUES

It seemed appropriate, in this presentation to an audience of scientists, to stress research opportunities. But as in the 1960's we increasingly recognize the issues created by scientific inquiry divorced from ethical and humanitarian considerations, it also seems appropriate we consider briefly what these studies, and especially the type mentioned in the last section, might mean to the Indian. We have no accurate census of the number of relatively pure Indians left in the Americas, nor of the greater number of persons of mixed but "substantial" Indian ancestry. Estimates of the order of 16,000,000 (17, 20, 24) have been made for the former, while the latter is easily several times that figure. We are talking about large numbers of people.

Who among us can read the history of the relations between the early settlers of his country and the Indian without deep shame for the barbarism heaped upon a people who were driven to defend the land they occupied. The world is watching my country as it agonizes over the Negro problem--it might equally well be watching the Americas for signs of a belated, moral resurgence with respect to the Indians. How satisfied are any of us with the official programs of our governments for the health, economic advancement, and education of the Indian? How can we translate the results of our scientific investigations into concrete action programs, programs which must be carefully related to other governmental measures. It is a dubious favor to lower infant mortality among the Indian without parallel economic measures to ensure food for the extra mouths. Nor does it seem likely that the accident-proneness of the Indian (refs. in 23), so easy to attribute uncritically to his heritage of violence and lack of familiarity with our gadgets, will yield to education until the frustrations which contribute to accident-proneness are relieved.

In a world which seems groping for perspective, the Indian provides a reference point from which to view the fantastic disruptions which modern men, intrinsically still little different in all essential biological attributes from Indians, have brought about. There are those who will take umbrage at my characterization of we representatives of Western Culture as "intrinsically still .... Indians." I am aware of the so-called intelligence tests which purport to show the inferior intellectual qualities of the American Indian, just as I am aware of similar results with respect to the American Negro. These results can and have been used as an excuse for less-than-equal schooling. But in both instances it is a matter of a culturally deprived and alienated group, perhaps also subjected to early nutritional deficiencies, whose role in impaired intellectual performance we are just beginning to recognize, being judged by tests designed by and standardized on a very different group (see also 4). By these remarks I do not mean to dismiss the possibility of intellectual differences between ethnic groups, but only to insist that to date the data are grossly inadequate, and we who call ourselves scientists must adhere to the null hypothesis, the more so since its various alternatives can be so conveniently misused by those who would evade their social responsibilities.

Be this last digression as it may, each time I return from the field, there is a period of culture shock as I realize how greatly in a short period of time we have contrived to disrupt our ecosystem, and our profound ignorance of the long range results of this disruption. Now in this time of greatly intensified concern over these problems, studies in depth of the Indian, within or without the framework of IBP, will surely contribute not only to his well-being but also to our own perspective and, eventually, the necessary adjustments towards which we are evolving.

REFERENCES

1. Arends, T., G. Brewer, N. Chagnon, M. Gallango, H. Gershowitz, M. Layrisse, J. Neel, D. Shreffler, R. Tashian, and L. Weitkamp. Intratribal genetic differentiation among the Yanomama Indians of Southern Venezuela. Proc. Nat. Acad. Sci. 57: 1252-1259, 1967.

2. Bearn, A. G., B. H. Bowman, and F. D. Kitchin. Genetic and biochemical considerations of the serum group-specific component. Cold Spring Harbor Symp. Quant. Biol. 29: 435-442, 1964.

3. Cavalli-Sforza, L. L., and A. W. F. Edwards. Analysis of human evolution. In: Genetics Today, vol. 3, S. J. Geerts (Ed.). Oxford, England: Pergamon Press, 1965, pps. 923-932.

4. Fischer, J. L. Letter to the editor. Perspectives in Biol. & Med. 11: 325-328, 1968.

5. Hackenberg, R. A. An anthropological study of demographic transition. Milbank Memorial Fund Quart. 44: 470-493, 1966.

6. Hanna, B. L. The biological relationships among Indian groups of the Southwest. Amer. J. Phys. Anthrop. 20: 499-508, 1962.

7. King, J. L. Continously distributed factors affecting fitness. Genetics 55: 483-492, 1967.

8. Lewontin, R. C. Population genetics. Ann. Rev. Genetics 1: 37-70, 1967.

9. Milkman, R. D. Heterosis as a major cause of heterozygosity in nature. Genetics 55: 493-495, 1967.

10. Mourant, A. E. The distribution of the human blood groups. Springfield, U.S.: C. C. Thomas, 1954, pps. 438.

11. Mourant, A. E., and A. C. Kopéc. The ABO blood groups: Comprehensive tables and maps of world distribution. Occasional publication no. 13 of Royal Anthropological Institute. Springfield, U.S.A.: C. C. Thomas, 1958, pps. 276.

12. Neel, J. V., and F. M. Salzano. A prospectus for genetic studies of the American Indian. Cold Spring Harbor Symp. Quant. Biol. 27: 85-98, 1964.

13. Neel, J. V., F. M. Salzano, P. C. Junqueira, F. Keiter, and D. Maybury-Lewis. Studies on the Xavante Indians of the Brazilian Mato Grosso. Amer. J. Hum. Genet. 16: 52-140, 1964.

14. Neel, J. V., and F. M. Salzano. Further studies on the Xavante Indians. X. Some hypotheses-generalizations resulting from these studies. Amer. J. Hum. Genet. 19: 554-575, 1967.

15. Neel, J. V., and N. A. Chagnon. The demography of two tribes of primitive, relatively unacculturated American Indians. Proc. Nat. Acad. Sci. 59: 680-689, 1968.

16. Neel, J. V., and W. J. Schull. On some trends in understanding the genetics of man. Perspectives in Biol. & Med., in press.

17. Rosenblat, A. La población indígena de América. Buenos Aires, Argentina: Institución Española, 1945.

18. Salzano, F. M. The blood groups of South American Indians. Amer. J. Phys. Anthrop. 15: 555-579, 1957.

19. Salzano, F. M. Studies on the Caingang Indians. I. Demography. Human Biol. 33: 110-130, 1961.

20. Salzano, F. M. Some genetic aspects of the demography of American Indians. In: Human Displacements, Entretiens de Monaco en Sciences Humaines, Première Session, J. Sutter (Ed.). Monaco: Imprimerie Nationale de Monaco, 1962.

21. Spuhler, J. N., and C. Kluckhohn. Inbreeding coefficients of the Ramah Navaho population. Human Biol. 25: 295-317, 1953.

22. Sanghvi, L. D. Comparison of genetical and morphological methods for a study of biological difference. Amer. J. Phys. Anthrop. 11: 385-404, 1953.

23. Schmitt, N., L. W. Hole, and W. S. Barclay. Accidental deaths among British Columbia Indians. Canad. Med. Assoc. J. 94: 228, 1966.

24. Steward, J. H., and L. C. Faron. Native peoples of South America. New York: McGraw-Hill Book Co., 1959.

25. Sved, J. A., T. E. Reed, and W. F. Bodmer. The number of balanced polymorphisms that can be maintained in a natural population. Genetics 55: 469-481, 1967.

26. World Health Organization Technical Report Series no. 279. Research on population genetics of primitive groups. Geneva, Switzerland: World Health Organization, 1964. 26 pp.