Heredity and society : proceedings / edited by Ian H. Porter, Richard G. Skalko. Assistant editors: Sally Kelly, Dwight T. Janerich.

Contributors

Symposium on Heredity and Society (1971 : Albany, N.Y.)
Porter, Ian Herbert.
Skalko, Richard G.
New York (State). Birth Defects Institute.

Publication/Creation

New York : Academic Press, 1973 [©1972]

Persistent URL

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HEREDITY AND SOCIETY

Edited by

IAN H. PORTER • RICHARD G. SKALKO

ACADEMIC PRESS

MONITORING, BIRTH DEFECTS AND ENVIRONMENT

THE PROBLEM OF SURVEILLANCE

Edited by ERNEST B. HOOK, DWIGHT T. JANERICH, and IAN H. PORTER

Assistant Editors: SALLY KELLY, and RICHARD G. SKALKO

1971, 324 pp.

This volume systematically considers methods for monitoring the incidence of malformations and mutations in the population in order to detect the introduction or increase of unsuspected mutagens and teratogens in the environment. It includes discussions of the rationale, problems, and costs of various approaches to this question, descriptions of several possible surveillance systems, and suggestions for improving, refining and elaborating monitoring. The markers discussed include fetal wastage, major malformations as well as tumors, minor malformations including dermatoglyphic abnormalities, protein changes, chromosome breaks and rearrangements, and other somatic mutations.

The book is based on the Birth Defects Institute Symposium held in Albany, New York, on October 19-20, 1970. It will be of interest to pediatricians, teratologists, geneticists, epidemiologists, cytogeneticists, biochemists, public health officials, and ecologists.

ADVANCES IN TERATOLOGY

VOLUME 5

Edited by D. H. M. WOOLLAM

1972, 185 pp., 13 plates.

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CONTENTS:

Academic Press
NEW YORK AND LONDON
111 FIFTH AVENUE, NEW YORK, N.Y. 10003
24/28 OVAL ROAD, LONDON NW1

ISBN 0–12–502850–1

HEREDITY AND SOCIETY

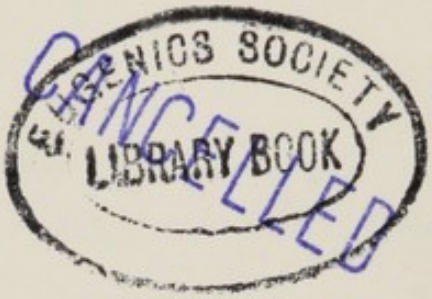
This book is a record of the second symposium sponsored by the Birth Defects Institute of the New York State Department of Health, held in Albany on October 26-27, 1971.

The purpose of the symposium was to focus attention on new knowledge and neglected problems in medical genetics. This volume explores the relationships between the science of genetics and modern life, i.e., the genetic problems engendered by various social trends and the possible contributions of genetics to the betterment of society. Topics discussed include:

- Genetics and civilization;
- Genetic change and evolution in humans;
- Genetic counselling of prospective parents;
- Genetic implications of industrialization and abortion;
- Birth defects and hereditary diseases.

The book will be of interest to geneticists, pediatricians, public health officials, teratologists, ecologists, and others—particularly those interested in the long-range impact of social trends on human populations.

Jacket design by Judy Gardonyi



HEREDITY AND SOCIETY

BIRTH DEFECTS INSTITUTE SYMPOSIA

Ernest B. Hook, Dwight T. Janerich, and Ian H. Porter, editors: MONITORING, BIRTH DEFECTS AND ENVIRONMENT: The Problem of Surveillance, 1971

Ian H. Porter and Richard G. Skalko, editors: HEREDITY AND SOCIETY, 1972

In preparation
Dwight T. Janerich et al., editors: PROBLEM OF CONGENITAL DEFECTS: New Directions, 1973

ACADEMIC PRESS RAPID MANUSCRIPT REPRODUCTION

HEREDITY AND SOCIETY

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IAN H. PORTER
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Assistant Editors

SALLY KELLY • DWIGHT T. JANERICH

Birth Defects Institute
New York State Department of Health
Albany, New York

Proceedings of a Symposium on Heredity and Society
Sponsored by the Birth Defects Institute of the
New York State Department of Health
Held in Albany, New York, October 26–27, 1971

ACADEMIC PRESS
New York and London
1973

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1

Library of Congress Cataloging in Publication Data

Symposium on Heredity and Society, Albany, N. Y., 1971.
Heredity and society; proceedings.

(Birth Defects Institute. Symposium series)
Sponsored by the Birth Defects Institute.
1. Medical genetics--Congresses. 2. Deformities--Genetic aspects--Congresses. I. Porter, Ian H., ed. II. Skalko, Richard G., ed. III. Birth Defects Institute. IV. Title. V. Series. [DNLM: 1. Genetics, Human--Congresses. 2. Hereditary diseases--Congresses. QH 431 S989h 1971]
RB115.S94 1971 616'.042 72-77366
ISBN 0-12-562850-1

PRINTED IN THE UNITED STATES OF AMERICA

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FOREWORD

This volume is a record of the second symposium held in Albany, New York on October 26 and 27, 1971, sponsored by the Birth Defects Institute of the New York State Department of Health.

This second symposium was attended by registrants from 16 different states across the country and from several Canadian provinces. Last year's symposium was equally well attended, but to me, the size and the caliber of this scientific group was of special significance. Many had returned for the second time, which seemed an indication that those who took part in the first symposium found it of value, as we certainly did.

Our Department has a long history of dedication to research. We have continued to seek new scientific knowledge and develop new techniques for improving people's health and well being. More than 40 percent of our operating funds go to support research in cancer, heart disease, kidney disease, and other critical areas. To this we have added the Birth Defects Institute, created by legislative action in 1967. The Institute investigates the causes and treatment of birth defects, conducts education and training programs, maintains a chromosome registry to aid physicians across the State in the diagnosis and treatment of birth defects, and provides counseling and referral services for parents with affected children. And, of course, it conducts symposia such as this.

The presentations from last year's program on the environmental causes of birth defects have been published by Academic Press.[1]

I think you will find the presentations in this volume thought-provoking and stimulating and that you will benefit greatly from the exchange of ideas in this medical discipline.

The function of these symposia is to focus the attention of health professionals on new knowledge in medical genetics—areas that most of the public knows of vaguely. We have chosen topics to consider and discuss, with which the medical scientists, in general, have not as yet come to grips, but

[1] The first volume: Hook, E. B., Janerich, D. T., and Porter, I. H. (Eds.), "Monitoring, Birth Defects and Environment– The Problem of Surveillance," Academic Press, New York and London, 1971, p. 308.

are about to—such as the genetic implications of population control and abortion—particularly in this State, where we have had over 200,000 abortions in the last year.

These are exciting and important questions and there will be a lot of discussion, now, and in the future—and possibly a few answers will evolve. The central theme, "Heredity and Society" means taking part in the exploration of the science of genetics as it affects and is affected by modern life. Obviously, there is much to be learned of this complex relationship. This symposium is part of that learning process and we sincerely hope that it will prove to be a valuable part.

Hollis S. Ingraham, M. D.
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ACKNOWLEDGMENTS

The Symposium upon which this volume is based could not have taken place without the expert administrative efforts of Edwin C. Jones and Sylvia Sickles. To them and the rest of the Staff of the Birth Defects Institute, and to Kathleen Decker and Ellen Heenehan for their assistance to the editors in the preparation and typing of the final manuscript, we express our thanks and appreciation.

SECTION I

GENETICS AND CIVILIZATION IN HISTORICAL PERSPECTIVE

Hymie Gordon

We are fortunate to be living in a period of great development in the basic science of genetics. In our time we have seen the discovery of the fundamental genetic material itself - not only the primary structure of the nucleic acids but their functionally crucial secondary and tertiary structures as well. Their functional pathology is being elucidated and they can be observed in action directly under the electron microscope. In our time it also has become possible to study the chromosomes of man in health and in disease, and techniques are being developed for examining their fine, submicroscopic structure. Also in our time, Garrod's prediction that differences between individuals are owing to differences in their vital chemistry is being fulfilled as the vast pattern of human biochemical variation is being unfolded. It is becoming feasible to observe the control of vital processes at the cellular, sub-cellular and molecular levels. Disease processes are being studied in the same way and soon we will be understanding many common diseases - infective, metabolic and neoplastic - in molecular rather than in histological terms. The interests of biochemists, cytologists and molecular biologists are overlapping more and more, and soon they will merge into a single comprehensive discipline of

Fundamental Biology.

Whenever major scientific advances are made, ethical problems arise. Historically this has occurred in connection with advances in astronomy, evolutionary biology and nuclear physics. The focus of the new developments in genetics is directed straight at the process of life itself and when their application to human affairs is considered, their potential role in the artificial control of the quality of human life inevitably comes to mind. Hence, it is not surprising that at the present time the new discoveries in genetics have provoked considerable ethical controversy and that the social responsibilities of scientists in general and of geneticists in particular are being debated probably with more vehemence than ever before.

As we join in this symposium on "Heredity and Society", it appears that we are still a long way from resolving the major ethical problems. To some it may seem that the problems are too new and ill-defined for us to be able to understand them adequately. However, when the historical development of some of these problems is considered and when we can examine them in the correct historical perspective, it may be that we will see them more clearly and understand them better. Possibly, experience in the past may help us to develop solutions for the present and for the future. It is my function in this symposium to provide such a historical perspective.

The science of genetics is a relatively new one: it is just over one hundred years old and most of the discoveries relative to its basic processes have been made within the last twenty years. But as an empirical art, the practice of genetics goes back much further because since the very beginning of civilization man has used genetic manipulation to improve the quality of his

life. In fact, "civilization" in the most fundamental sense of that term owes its beginning to man's earliest interest in genetics.

I. THE BEGINNING OF GENETICS AND CIVILIZATION

The history of civilization and the history of genetics both began about 10,000 years ago in the Neolithic period. The first clear archeological records of that period were found in the territory of what is now Israel, on the slopes of Mount Carmel and, more substantially, in the Jordan Valley in the district of Jericho.[1] In that part of the world, 10,000 years ago, the climate was changing. The heavy, persistent rains of what the geologists call the Pluvial period had ceased and were being replaced by the dry, dusty climate which we now associate with the deserts of Judea. Primitive man in these territories was a nomadic hunter and gatherer; he had no crops or flocks, and he moved ceaselessly across the desert searching for water and for whatever wild animals and wild plants he needed for his sustenance.

It was a precarious existence, and it is unlikely that human life could have survived indefinitely under these circumstances. Then, 10,000 years ago, an unnamed prehistoric genius recognized that he could save himself much trouble and secure a much more secure life for himself and for his family if he were to plant his own crops near a constant source of water. Perhaps the vegetation round the perennial spring of fresh water at Jericho first suggested this to him.

During their wanderings, our Neolithic genius and the members of his band had developed a taste for certain kinds of wild grain which were not available at Jericho. So they brought seeds and

seedlings to Jericho and planted their first crops. Having done so, they had to wait through the season for the crops to ripen. The crops had to be protected from human and other predators so fences were built round them. The local fauna, the wild animals which were also attracted by the fresh water, provided additional food for the Neolithic band and to ensure regularity of this supply, animals were captured alive and fenced in. The captive animals mated and reproduced, thus enlarging the herds.

These elementary attempts at domesticating wild grasses and wild sheep and goats were successful, so it was no longer necessary for the Neolithic band to wander far and wide in search of food. They became more discriminating about which grains and animals they cultivated. They selected those forms of wheat and barley which were more prolific grain-producers and easier to harvest with their stone sickles, and within a few seasons they produced flourishing crops of edible cereals.[2] Wild sheep have coarse, hairy coats, but Neolithic man noticed that occasional mutants have soft woolly fleeces. He selected these mutants for preferential breeding, and soon he had fine flocks of woolly sheep to provide a constant supply of both clothing and meat.[3]

The crops and flocks demanded constant attention and compelled Neolithic man to give up his nomadic life-style. Instead, he and his fellows concentrated on developing more permanent dwellings, replacing their flimsy temporary shelters by more substantial houses of wood, stone and clay. The more settled living and dependable food supply had an immediate beneficial effect on the health and population growth of the group, and soon there was a local population explosion. Archeologists have estimated that this first Neolithic settlement at Jericho

occupied an area of about ten acres with a population of about 2,000; so there must have been quite an elaborate system of irrigation to ensure an equable distribution of the spring water.[1] The growing prosperity of the settlement made it vulnerable to attack, so it was necessary to build a massive stone defensive wall and at least one great lookout tower.

Remains of these structures have been unearthed by the archeologists. They have also found some of the tools which Neolithic man used for harvesting his crops.[1] In the early Neolithic levels they have found specimens of emmer wheat and two-row barley, both of which are cultivated crops.[4] They have found skeletal remains of small-boned, presumably domesticated cattle, goats and pigs. And they have found skeletal remains of Neolithic man himself and examples of some of his idols.[1] The evidence for the transition at Jericho of Neolithic man from a nomadic hunter-gatherer to a settled farmer who practiced selective breeding is indirect because there are no written records, but the archeological evidence is most convincing.

The supervision of the irrigation system and the building of the great wall and tower must have required quite a sophisticated communal organization and administration. And so, quite suddenly on the prehistoric time-scale, Neolithic man found himself to be a citizen of a substantial town. The Latin word for a town is civitas, and civis is a citizen. Civilis, in Latin, means "relating to being a citizen"; hence, our word civilization.

Thus, my assertion that man's interest in genetics marked the beginning of civilization is a demonstrable fact of history, or rather of prehistory. I have cited the evidence from Neolithic Jericho. Similar evidence is available

from the Neolithic settlement at Catal Hüyük in Anatolia.[5] Preliminary findings at the Spirit Cave site in Northern Thailand also attest to the interdependence of settlement and agriculture selection.[6]

II. THE SELECTIVE BREEDING OF ANIMALS IN ANTIQUITY

Archeology and the written records of early civilizations provide numerous examples of man's early interest in plant and animal breeding and its successful application. The earliest identified "pedigree chart" is a clay tablet inscribed with pictographic symbols probably relating to the breeding of horses. It was found in the district of Susa in Iran and dates from the Proto-Elamitic period, about 3100 B.C.E.[7]

A Bibical Example

The Bible gives a detailed account of the Patriarch Jacob's selective breeding of sheep and goats (Genesis 30, 25-43). At that time, in about 1675 B.C.E., Jacob was working on his uncle and father-in-law Laban's farm in Haran in what is now Syria. Laban had agreed to pay Jacob his wages in kind: to give him all the black lambs and all the brindled and spotted goats; but later Laban tried to cheat Jacob. To protect his own interests Jacob peeled strips of bark off branches of poplar, almond and plane trees so that the white wood showed through. He placed these at the watering places so that the animals would have them in sight while mating; then the she-goats gave birth to young that were striped, spotted and brindled.

This remarkable achievement of intra-uterine impression defies rational explanation, but Jacob's subsequent actions make good sense. It is recorded (Genesis 30, 40) that "As for the

rams Jacob divided them, and let the ewes run only with such of the rams in Laban's flocks as were striped and black; and thus he bred separate flocks for himself, which he did not add to Laban's sheep". Jacob's genetic enterprise was rewarding: "So Jacob increased in wealth more and more until he possessed great flocks, male and female slaves, camels, and asses." (Genesis 30, 43)

Homeric Greece

A passage in the Iliad, written in about 900 B.C.E., shows that in Homeric Greece the importance of selecting the appropriate stock for successful horse breeding was well-recognized (Iliad V, 260-274). During an episode in the Trojan war, Diomedes the Achaean tells his companions of a remarkable breed of horses owned by his adversary Aeneas of Troy. "....they are bred from the same stock that all-seeing Zeus gave Tros in return for his boy Ganymedes; and they were the best horses in the world. Later Prince Anchises stole the breed by putting mares to them without Laomedon's consent. The mares foaled in his stables, and of the six horses that he got from them, he kept four for himself and reared them at the manger, but he gave these two to Aeneas for use in battle. If we could capture them, we should cover ourselves with glory."[8] In the subsequent battle Aeneas was wounded by Diomedes and his horses were seized and brought back to the Achaean camp as a great prize.

The Roman World

In the Roman world animal breeding was practiced extensively. Virgil, writing in the first century B.C.E., poetically but with fine attention to detail, gives valuable advice on the selection of sires for horse breeding and the

selection of calves for cattle breeding (Georgics III, 40-230). For example, he exhorts his readers: "When the lusty youth of thy flock endures, let loose the males, put thy herds early to breeding, and generation by generation keep up the succession of thy stock."[9]

III. MODERN ACHIEVEMENTS IN AGRICULTURAL GENETICS

Throughout the centuries, empirical experience has guided the breeding programs of farmers. Only in this century with the discovery and application of the Mendelian Laws of Inheritance has this activity become scientific. In many instances the results of this scientific progress have been spectacular and there is every reason to be grateful to the agricultural geneticists for their contribution to the improvement of the quality of human life. I shall describe just two examples.

High-Lysine Maize

In many underdeveloped communities, in Africa and in South America, corn or maize is the staple article of diet. Unfortunately, maize does not contain all the essential amino acids: it is especially poor in lysine. Hence, children raised on predominantly maize diets do not develop adequately: their growth is retarded, their susceptibility to infection is increased and there may be impairment of their intellectual development. In the more acute phases of such malnutrition, fatty enlargement of the liver, peripheral neuropathy and the syndrome of kwashiorkor may occur. The production of a strain of maize with a higher lysine content would clearly be desirable in these areas.

Workers at Purdue University examined the lysine content of a number of mutant varieties of maize.

One of these, called opaque-2, was found to have a significantly higher lysine content: 3.4 g. of lysine per 100 g. of protein in opaque-2 maize endosperm compared with 2.0 g. per 100 g. in ordinary maize endosperm.[10] When weanling rats were fed with opaque-2 maize, they gained an average of 97 g. in 28 days, compared with an average weight-gain of 27 g. in weanling rats fed with ordinary maize.[11] Dr. Oliver E. Nelson of the Department of Genetics at the University of Wisconsin has informed me that preliminary results in human subjects are most promising. Opaque-2 maize ("high lysine corn") has been found to be at least as effective as milk protein in promoting the growth of children, in correcting kwashiorkor, and in maintaining adults in nitrogen balance.[12] If its early promise is fulfilled, this mutant maize may contribute greatly to the promotion of health in underdeveloped countries.

Improving the Rice Plant

Similar success has been obtained with rice breeding. In South-East Asia, the tall Indonesian "Peta" variety of rice is extensively cultivated. It has the advantages of being disease-resistant and of producing vigorous seedlings. It is also multi-tillered; that is, it has many ears on a single stalk. Unfortunately, when attempts are made to increase production by using fertilizers, the rapid growth of the plant leads to trouble: wind and rain knock over the tall brittle stalks and ruin the crop. Plant geneticists at the International Rice Institute in the Philippines have sought to correct this weakness in "Peta" rice by crossing it with shorter, sturdier strains.[13] In one trial they crossed the "Peta" variety with a short Chinese "Dee-geo-woo-gen" variety. The latter is

a poor quality plant, low-tillered and disease susceptible with relatively poor seedling vigor; but it has the advantage of a short, sturdy stalk. After four generations of selective crossing of these two varieties, a strain of rice was produced with most of the advantages of both parental strains. This "IR 8 strain" is short and multi-tillered with stiff straw; it is disease resistant and has good seedling vigor. Several similarly improved varieties of rice are now being investigated in Asia; the results so far are highly satisfactory and major benefits for the rice-eating peoples can be expected.

IV. THE CONTROL OF HUMAN BREEDING IN ANTIQUITY

Long before he had learned the biological principles of heredity and long, long before he had discovered the nature of the genetic material and its mechanism, man began to apply his empirical knowledge of genetics, derived from his agricultural experience, to human affairs. Early historical records testify to man's concern about hereditary implications in his social, economic and political life. For instance, the Bible contains many references to problems of consanguinity.

The Genealogy of the Patriarchs (the numbers with asterisks refer to Figure 1.)

The family history of the Patriarchs includes several consanguineous marriages. Their progenitor Terah I.2*, who came from Ur in Southern Babylon, had at least two wives. By one of them I.3* he had three sons, Abraham II.2*, Nabor II.3* and Haran II.4* (Genesis 11, 27); by the other II.1* he had a daughter, Sarah II.1*. Thus, when Abraham married Sarah, he married his half-sister (Genesis 20, 12): Isaac was the son

of this marriage (Genesis 21, 3). Abraham's brother Nahor married Milcah III.2*, the daughter of the third brother, Haran (Genesis 11, 29). The child of this uncle-niece marriage was Bethuel (Genesis 24, 15). Abraham had left the family home in Haran, Syria, to settle in Canaan, but when the time came for Isaac to take a wife, Abraham instructed his servant to go back to Haran "to my own country and to my own kindred to find a wife for my son Isaac." (Genesis 24, 4). The young woman who was chosen was Rebecca IV.1*, the daughter of Isaac's first cousin, Bethuel (Genesis 24, 15): thus, Rebecca was Isaac's paternal first-cousin-once-removed.

Isaac and Rebecca were the parents of a pair of apparently dizygotic male twins, Esau VI.1* and Jacob VI.2* (Genesis 25, 24-26). Isaac followed the family tradition by forbidding Jacob to marry one of the local Canaanite girls and sent him back to the ancestral homeland to seek a wife (Genesis 28, 2). There he worked for his maternal uncle Laban V.2* (Genesis 28, 5) and married his uncle's daughters - his maternal first cousins - Leah VI.3* and Rachel VI.4* (Genesis 29, 32-35 and 30, 18-21). Isaac's marriage to Leah produced six sons and a daughter VII.1-7*: Reuben, Simon, Levi, Judah, Issachar, Zebulun, and Dinah (Genesis 29, 32-35 and 30, 18-21). Isaac's marriage to Rachel produced two sons: Joseph VII.8*, (Genesis 30, 22-24) and Benjamin VII.9*, (Genesis 35, 16-18).

Thus, Abraham, Isaac and Jacob all married consanguineously; to a half-sister, to a first-cousin-once-removed, and to a first cousin respectively.

Lot and His Daughters

A more remarkable instance of consanguinity occurred in the case of Lot, Abraham's nephew

(Genesis 19, 30-38). When the destruction of Sodom and Gomorrah was imminent, Lot fled with his two daughters and eventually took refuge in one of the Dead Sea caves. Cut off from all other human contact, Lot's daughters plotted to have intercourse with their father so that they could have children - "to sustain the continuity of life through our father". Each daughter became pregnant and gave birth to a son. The older daughter called her son Moab which she derived from the Hebrew mē āb meaning "from father". The younger daughter called her son Ben-ammi which means "son of my kin". Moab and Ben-ammi were the traditional progenitors of the Moabites and ammonites.

The desolate setting of this melodrama in a deserted cave in the bleak Judean hill country with the distant sky lit up by the flaming brimstone of Sodom and Gomorrah, and the restrained style of the Biblical narrative successfully achieve a sense of profound horror in describing this primitive act of incest. Interpreters through the centuries have disagreed over the purpose of this narrative. Some believe that it is included in the Bible simply to throw scorn on the ancestry of the Moabites and Ammonites who became traditional enemies of Israel. Others believe that its purpose is to emphasize that even this most extreme action is justified if it is the only way to ensure the continuity of human life.

Forbidden Matings

In the later evolution of the Israelite nation, legislation was introduced to prohibit the mating of close relatives (Leviticus 18, 1-18). The Israelites were specifically exhorted to reject the consanguineous practices which were common among the Egyptians and Canaanites (Leviticus 18,

1-3). The fundamental principle on which the new marriage laws were based was stated quite explicitly: "No man shall approach a person of his same flesh for sexual intercourse" (Leviticus 18, 6). This may seem to imply concern for genetic relationships but as will be seen in Table 1, the prohibitions included in-laws and other non-genetic relatives as well. In the genetic group, the prohibition included only first and second degree relatives. In fact, marriages between third degree relatives (first cousins) were sometimes encouraged; this is exemplified by the case of the daughters of Zelophehad.

The Daughters of Zelophehad (Numbers 27, 1-11; and 36, 1-13)

Zelophehad, a member of the Gilead clan of the Manasseh tribe, was a wealthy man who died during the Israelite wanderings in the desert. He left no sons but he had five unmarried daughters who inherited his patrimony. The heiresses were greatly in demand and their relatives were worried by the prospect of the girls marrying out of the Manasseh tribe and taking much of the tribal wealth with them. The heads of the Gilead clan brought their problem to Moses and his council of chiefs. Moses, instructed by the Lord, gave the following ruling:

"....the daughters of Zelophehad....may marry whom they please, but only within a family of their father's tribe. No patrimony in Israel shall pass from tribe to tribe, but every Israelite shall retain his father's patrimony. Any woman of an Israelite tribe who is an heiress may marry a man from any family in her father's tribe." (Numbers 36, 6-8)

The Bible records that the heiresses accepted this ruling by marrying their first cousins: "Mahlah, Tirzah, Hoglah, Milcah and Noah....

married some of their father's brothers. They married within the families of the sons of Manasseh son of Joseph, and their patrimony remained with the tribe of their father's family." (Numbers 36, 11-12)

It may be that this tradition of marrying within the clan has resulted in a greater coefficient of inbreeding among modern Jewish communities than is realized. This may be a partial explanation of the relatively high frequency of certain diseases with autosomal-recessive patterns of inheritance among modern Jewish communities of the Ashkenazi group. Tay-Sachs disease, familial dysautonomia, torsion dystonia and Niemann-Pick disease have a greater incidence in Ashkenazi Jews than in Gentiles. Consanguinity of the parents is seldom recognized but generations of inbreeding among the ancestors may have resulted in a closer genetic relationship of the parents than is realized.

Population Quality Control in Classical Greece

According to tradition, the power of Sparta and its martial constitution were created by Lycurgus who ruled in the Ninth Century before Christianity. Plutarch's Life of Lycurgus describes how human breeding was controlled to further Spartan imperial aspirations. Plutarch records that "....Lycurgus was of a persuasion that children were not so much the property of their parents as of the whole commonwealth, and, therefore, would not have his citizens begot by the first-comers, but by the best men that could be found".[14]

Only matings of the fit were permitted and the sole purpose of marriage was to produce healthy children for the State. But even the formality of marriage was not a barrier to a mating which might provide desirable issue. "....an honest man who had love for a married woman upon account

of her modesty and the well-favouredness of her children, might, without formality, beg her company of her husband, that he might raise as it were, from this plot of good ground, worthy and well-allied children for himself."[14]

The parents had no say in the disposition of their newborn child. The father had to bring the baby before a panel of judges at a place called Lesche. If they found the baby "stout and well made" they gave orders for its rearing and provided for its maintenance; but if they found the baby to be "puny and ill-shaped", they ordered it to be taken away and exposed at the Apothetae, a sort of chasm under Mount Taygetus.[15]

This was in primitive Sparta, usually characterized as a tough, anti-intellectual, anti-aesthetic militaristic society - the antithesis of the culturally progressive Athens, home, in the Fifth Century B.C.E., of some of the greatest writers, artists, statesmen and philosophers of all time. Yet one of its brightest luminaries, Plato (c 429-347 B.C.E.), expounded ideas about human breeding surprisingly similar to those of Lycurgus the Spartan. In his book, the Republic, Plato has his mentor Socrates - scourge of the establishment and idol of the young - challenge Glaucon to agree that just as it is important to be careful in the breeding of hunting dogs and birds, so should the State be careful in its control of human breeding. He goes on to propose the preferential mating of selected young men: "....our braver and better youth, besides their other honours and rewards, might have greater facilities of intercourse with women given them; their bravery will be a reason, and such fathers ought to have as many sons as possible." (Republic V. 460b)[16]

It is noteworthy that Lycurgus had also used the argument that if people were so solicitous

about the selective breeding of their dogs, they should be at least as selective when it came to breeding children. And Plato similarly agreed with the Spartan practice of destroying unsatisfactory babies:

"The proper officers will take the offspring of the good parents to the pen or fold, and there they will deposit them with certain nurses who dwell in a separate quarter; but the offspring of the inferior, or of the better when they chance to be deformed, will be put away in some mysterious unknown place, as they should be." (Republic V. 460c)[17]

Plato, uncharacteristically, leaves to our imagination the details of the actual process to be used in "putting away" these unfortunate babies.

V. EUGENICS IN RECENT WESTERN SOCIETY

As far as is known, the Platonic proposals for human quality control were never accepted in Classical Greece. The subject was frequently revived and debated in European society throughout the subsequent millenia. They were particularly popular in Nineteenth Century Germany, both in philosophical and in scientific circles.

Friedrich Nietzche (1844-1900)

A leading philosophical exponent of directed human breeding was Friedrich Nietzche, once Professor of Classic Philology at the University of Basel. His best known work, Also Spracht Zarathustra was written during a period of serious ill health which progressed to an ultimately fatal psychotic and paralytic organic brain syndrome. In this work recurring themes are the rejection of the "old morality", a call for a "new morality", and the ideal of the Superman -

an ideal to be achieved by carefully selected matings:

"Creative thirst, an arrow of desire for the Superman: say, my brother, is this thy will to marriage?

Holy call I such a will and such a marriage.

Thus spake Zarathustra."[18]

Ernst Haeckel (1834-1919)

The leading scientific proponent of these ideas was Ernst Haeckel, Professor of Zoology at the University of Jena. He was an enthusiastic Darwinian and sought to apply the concept of "survival of the fittest" to the human species. He deplored the role of physicians in sustaining the lives of patients with tuberculosis, syphilis and mental disease. According to Haeckel these diseases "are transmitted by inheritance to a great extent" and by keeping their patients alive, physicians were promoting the spread of these diseases to subsequent generations. He stated that mental disease and chronic physical disease were increasing in frequency and that to stop this the present generation of the diseased had to be eliminated.[19] He proposed a commission to decide which of the diseased and disabled should live and which should die. Those deemed undesirable by the commission should be granted "redemption from evil....by a dose of some painless and rapid poison".[20] He did not specify the poison or who should administer it. It was Haeckel's position that rather than supply nursing homes, therapeutic and rehabilitation facilities for the disabled, legislation should be introduced to allow these unfortunates to be killed off.

The tall blonde "Aryan" was Haeckel's ideal human breeding stock and he produced what he called "historical evidence" to substantiate this

notion. For example, he cited the origins of Jesus of Nazareth. Haeckel had rejected his earlier faith in Christianity but recognized that there were some commendable qualities in the character and teachings of Jesus. These good traits could not possibly be derived from Jesus's Semitic mother so Haeckel turned for help to a scurrilous piece of anti-Christian propaganda, the Book of the Genealogy of Jesus. The pseudo-gnostic author of this book claimed that Joseph Pandera, a Roman soldier, seduced Mary of Bethlehem and was the father of Jesus. This Roman soldier was somehow Hellenized by Haeckel and hence, satisfied Haeckel's insistence that Jesus's good qualities were "certainly not Semitical" but were inherited from a member of "the higher Arian race, and especially of its noblest branch, the Hellenes".[21]

This is a fairly representative sample of Haeckel's historical and biological thinking. It may seem ridiculous to us today but at the turn of this century, Haeckel was regarded by many as the most eminent biologist of the era. Bismarck was influenced by him as were the founders of the Nazi movement in the Twentieth Century. The Monist League which Haeckel organized to help propagate his ideas received generous support from the German industrialist Alfred Krupp;[22] and some of Krupp's descendents later in the Twentieth Century contributed substantially to the finances of the Nazis.

In England, Charles Darwin maintained a friendly correspondence with Haeckel whose support for the evolutionary theory he appreciated and whose knowledge of systematic biology he admired.[23] Darwin himself did not extrapolate from his concept of the "survival of the fittest" to a program of selective human breeding. One wonders how his cautious mind would have reacted

to the bizarre theological and sociological ideas which Haeckel presented in Die Weltratsel ("The Riddle of the Universe") published in 1899, about 17 years after Darwin's death.

Francis Galton (1822-1911)

It was Darwin's paternal half-cousin, Francis Galton, who popularized the idea of improving human stock in England. He introduced the term eugenics to designate the science of improving the human stock, not only by selective breeding but by other processes as well. He explained what he meant by "eugenics" in the following way:

"We greatly want a brief word to express the science of improving stock, which is by no means confined to questions of judicious mating, but which, especially in the case of man, takes cognizance of all influences that tend, in however remote a degree, to give to the more suitable races or strains of blood a better chance of prevailing speedily over the less suitable than they otherwise would have had. The word eugenics would sufficiently express the idea; it is at least a neater word and a more generalized one than viriculture, which I once ventured to use."[24]

Galton's reference to "viriculture" reveals the association in his mind between agricultural achievements and programs for selective human breeding. In fact, in one of his essays he directly compared the breeding of race horses with the breeding of humans.[25] Galton had been much impressed by his studies of the genealogies of men of distinction in Science, Arts, Politics, etc. and concluded that hereditary influences made a major contribution to their success.[26] He suggested a system of marks for "family merit", based on the achievements of the recent male

ancestors, for assessing the suitability of young men for public service appointments. "I cannot doubt," wrote Galton, "if two youths were of equal personal merit, of whom on belonging to a thriving and long-lived family, that there could be any hesitation in saying that the chance were greater of the first-mentioned youth becoming the more valuable public servant of the two."[27]

Galton's ideas received wide-spread support and the University of London approved of them to the extent of establishing a Laboratory for National Eugenics with Galton as its first director. Despite his enthusiasm for heredity, Galton always maintained a reasonably balanced view of the relevant roles of "nature and nurture" - an expression which he borrowed from Shakespeare[28] and turned into a colloquialism of modern biology. It was his belief that nature prevailed over nurture but only "when the differences of nurture do not exceed what is commonly to be found among persons of the same rank of society in the same country".[29] In other words, only when environmental factors were approximately equal, could differences between individuals be attributed to hereditary influences.

Karl Pearson (1857-1936)

Galton's eugenics were always positive; that is, he was in favor of improving human stock by encouraging desirable matings. At no time did he advocate negative eugenics - the killing, sterilization or segregation of genetically undesirable individuals. His successor as director at the Galton Institute of Eugenics, Karl Pearson, on the other hand was a vociferous proponent of negative eugenics.

Pearson, an economist turned biostatistician, rejected the newly re-discovered mendelian

genetics, preferring Galton's biometrical concept of continuous or blended genetic variation. Unlike Galton, his attitude to "nature and nurture" was narrow-minded. In discussing the development of human ability, he asserted that "....it is quite safe to say that the influence of environment is not one-fifth that of heredity, and quite possibly not one-tenth of it."30

Pearson warmly endorsed Plato's proposals for a governmental program of negative eugenics. In the course of a lecture at Oxford, Pearson said: "Now may we not claim Plato as a precursor of the modern Eugenics movement? He grasped the intensity of inheritance for he appeals to the herd and the flock; he realized the danger to the state of a growing band of degenerates, and he called upon the legislator to purify the state."31

Pearson followed the precedent set by Plato, Haeckel and Galton in jumping straight from the breeding of cattle to the breeding of man. He shied from making specific recommendations to ensure that "undesirables" did not have children but he did drop a few hints in passing the responsibility from the scientist to the legislator:

"....every remedy which tends to separate (the criminal, the tuberculous, and the neurotic) from the community, every segregation which reduces their chances of parentage, is worthy of consideration..... The duty of the man of science is to find out the (biological) law, and if possible waken the conscience of his countrymen to its existence. It is the function of the statesman to discover the feasible social remedy which is not at variance with this law."32

Many families with inherited diseases were studied at the Laboratory for National Eugenics some of which were reported by Pearson. It is

hoped that he was not involved in genetic counselling. In describing a family with the cleft hand and foot anomaly, he expressed annoyance at the index patient for having born several affected children; he referred to her angrily as "this Lobster-Claw woman" and a "tramp".[33] He was equally scathing in his reference to a young man with hemophilia who recently had become engaged and who sought advice about the heritability of the disease. "Neither of these young people", wrote Pearson, "seems to have considered that both had moral responsibility to their unborn children and to their nation before they got engaged."[34] I wonder what he had to say to the young couple themselves.

Charles Davenport (1866-1944)

Pearson's counterpart in the United States was Charles Davenport, director of the Station for Experimental Evolution and the Eugenics Record Office at Cold Spring Harbor, Long Island, New York. He disagreed with Pearson by enthusiastically endorsing mendelian genetic principles against Pearson's "biometric" approach but in most other respects these two directors of Eugenic Institutes had very similar ideas. Like Pearson - and, in fact, like most other writers on human genetics in the early years of the Twentieth Century - Davenport had a penchant for making sweeping generalizations about the inheritance of human behaviour, ability, health and disease based on the investigation of a few selected pedigrees. Like Pearson in England, he was concerned about the effect of immigration on the genetic constitution of his countrymen. He welcomed immigrants from Germany, Poland, Scandinavia; had mixed feelings about Austro-Hungarians, Italians and Irish; and deplored the influx of "Hebrews".[35] He summarized his views on

immigration by stating that:
"....unless conditions change of themselves or are radically changed, the population of the United States will, on account of the great influx of blood from South-eastern Europe, rapidly become darker in pigmentation, smaller in stature, more mercurial, more attached to music and art, more given to crimes of larceny, kidnapping, assault, murder, rape and sex-immorality and less given to burglary, drunkness and vagrancy than were the original English settlers."[36]

Davenport, a zoologist by training, followed the pattern of European eugenists by equating human breeding with agricultural genetics. He warned of the imminent danger of the biological degeneration of the human race in general and of the American nation in particular if human breeding was allowed to proceed without control. He proposed a program for "The Salvation of the Race through Heredity":

"The experience of animal and plant breeders who have been able by appropriate crosses to increase the vigor and productivity of their stock and crops should lead us to see that proper matings are the greatest means of permanently improving the human race - of saving it from imbecility, poverty, disease and immorality."[37]

Davenport's eugenic activities were financially supported by members of the Harriman, Rockefeller, Huntington and other well-known American families. During the first three decades of this century, Davenport and his ideas were very fashionable but in the 'thirties, when events in Europe demonstrated the disastrous implications of a national eugenics program, Davenport lost most of his followers and sponsors. The Carnegie Institution, which had helped to establish Davenport's facilities at Cold Spring Harbor, withdrew its support in 1940.[38]

The Eugenic Sterilization Law in Nazi Germany

Pearson's and Davenport's eugenic proposals were never accepted officially by the governments of Britain or of the United States, but in Nazi Germany both negative and positive eugenics became State policy. Positive eugenics was promoted mainly by official encouragement and a system of awards. Negative eugenics, which in the pre-war period was achieved mostly by sterilization of "undesirables", was enforced by an elaborate legal mechanism.[39]

The first step in the legal process was taken by the District Health Officer (Bezirksartz). If a mentally subnormal or otherwise defective person was brought to his attention, it was his responsibility to investigate the case and, if appropriate in his opinion, submit a proposal (antrag) for sterilization to the Local Eugenic Court (Erbsgesundheitsgericht). This court, consisting of a lawyer and a medical geneticist, would review the proposal and either reject it or recommend sterilization. If the person in question disagreed with the local court's decision, he was entitled to an appeal to a Higher Eugenic Court (Erbsgesundheitsobergericht) whose decision was final. At each stage of the proceedings, expert and lay witnesses would be introduced and cross-examined and considerable use was made of medical records and family history.

Legislation was also introduced to control marriages. The Law for the Protection of the Genetic Well-being of the German people (Gesetz zum Schutze der Erbgesundheit des deutschen Volkes) banned marriage when one of the parties was regarded as unsuitable because of mental disorder, inherited disease or racial origin.[39]

It must be emphasized that these processes were strictly legal and a matter of common public

knowledge; they had at least the tacit approval of a majority of the legal and medical professions. Geneticists, and particularly medical geneticists, played important roles in the implementation of these laws by investigating family histories, by giving expert evidence in the courts and by participating judicially in the Eugenics Courts themselves. A number of human geneticists publically expressed their approval of the system; for example, Professor Otto von Verschuer of the University of Munster, in a book entitled Leitfaden der Rassenhygiene (1941), wrote:

"Decisive for the history of a people is what the political leader recognizes as essential in the results of science and puts into effect. The history of our science is most intimately connected with German history of the most recent past. The leader of the German state is the first statesman who has wrought the results of genetics and race hygiene into a directing principle of public policy."

In 1962, Professor L.C. Dunn of Columbia University quoted these words in his Presidential Address to the American Society of Human Genetics.[40] Von Verschuer responded by expressing his dismay on re-reading what he had written: "I now realize the errors on which such premature formulations were based...."[41] He added that he had publically altered his attitude, saying that "All intentions of race betterment by means of sterilization are to be rejected" and "the past has given a horrifying example of misused genetics."

While not doubting the sincerity of Professor von Verschuer's change of heart, it is to be regretted that not many of the victims of the "premature formulations" were available to accept his apology.

VI. HUMAN GENETICS TODAY AND IN THE FUTURE

The advances made in the basic sciences of genetics have been accompanied by progress in the clinical practice of genetics. There is greater precision of diagnosis thanks to developments in cytology and biochemistry; there is better understanding of disease processes; and there are increased opportunities for treatment. The prevention of hemolytic disease of the newborn caused by maternal-fetal rhesus incompatibility is an outstanding example of genetics positively applied to the improvement of human life. The effective use of prophylactic anti-D gamma globulin has to a great extent controlled the ravages of what was until recently a major cause of disease and death in infancy.[42] This is a discovery which, in historical perspective, could rank amongst the greatest achievement of modern medicine.

I would like to record that positive achievements of this sort represent the aspirations of most workers in human genetics today. Unfortunately, this is not so. Despite horrifying experiences of the recent past, there is still too much emphasis today on negative aspects of genetics - on sterilization and abortion. As we meet for this symposium there is a great deal of enthusiasm for the new technique of amniocentesis: for the intrauterine diagnosis and consequent destruction of unacceptable babies. Apart from the moral issues, I believe the practical utility of amniocentesis - its indications, its safety, and its diagnostic reliability - have grossly been overestimated. I am surprised at the uncritical acceptance of this procedure by so many of my colleagues. I do not recommend amniocentesis myself and this attitude, so far, has had no influence on my clinical practice in

genetics.

My opposition to amniocentesis is in part practical and in part owing to my absolute rejection of abortion in the ethical practice of medicine. I will not destroy any human life at any time after its conception even if I suspect that the individual may be less than perfect mentally or physically; I will not destroy a human life myself nor will I request or advise or encourage anyone else to do it for me. And I will not put the mother into the agonizing position where she must decide whether her unborn baby shall be killed or whether it may be allowed to continue to live.

I reject, with contempt, the inhuman attitude recently advocated by the Committee on Science and Public Policy of the National Academy of Science and published under the editorship of the President of the Academy:

"Relatively simple surgical procedures permit determination of the sex of the young fetus. A family which desires to limit its size should be permitted the option of such inspection and, having one boy, for example, abort the next fetus if it is not a girl."43

A great deal is being said and written today about "legal" abortion and about "legislation" to facilitate abortion. The eugenic sterilization program in Nazi Germany was <u>legal</u> and it was introduced by the regular legislative processes. It was legal but it was not <u>moral</u>. Surely the concern of we geneticists and humanitarians should be the morality of a procedure and not merely its legality. Human genetics, because of its close association with the fundamental process of life, is especially vulnerable to abuse, as my review of the eugenic movement has shown. We must continually be on our guard against those who seek to abuse it in our time, even if they

are amongst the mightiest in our land.

Priorities for Human Genetics

To complete the historical perspective, I offer you a personal list of priorities for human genetics in the immediate future. I emphasize that it is a personal list which many other practicing human geneticists could improve or supplement.

Firstly, we need better and more extensive facilities for the management of patients with genetic diseases or birth defects. Facilities in this country for the care and habilitation of children with mental sub-normality, for example, are inadequate. The developmental potential of many of these children is seldom fully realized. The primary concern of these facilities should be for the immediate welfare of the patients, but their potential for research into the treatment and prevention of birth defects and genetic diseases should also be recognized.

A second priority should be more education for the medical professions, for the health professions generally, and for the public at large in respect of genetic matters. The clinical practice of genetics is developing rapidly and there is an urgent need for training programs and working facilities for personnel in genetics counselling, diagnosis and treatment. Genetic counselling is the only realistic approach presently available for an acceptable eugenics program. Its success depends heavily on the education of the counsellors and of the population at risk.

The third priority is for greater attention to be paid by medical geneticists to the common diseases of medical practice: to ischemic heart disease, hypertension, strokes, cancer, diabetes, glaucoma, the common psychoses and others. Medi-

cal genetics is still too much concerned with rare and exotic diseases with their comparatively tidy mendelian patterns of inheritance. A great deal of the nation's research potential, in money and in manpower, is being spent on the study of these rare diseases, with the tempting prospect of a cure being found by manipulation of the genetic material. I have already expressed my excitement and awe at the achievements of molecular biologists and their contributions to our understanding of the vital processes. But I must admit to some disappointment, after earlier enthusiasm, at the prospects for cures of genetic diseases by genetic engineering in my lifetime or in the lifetime of my patients; I hope that events will prove me wrong. In any event, there is no reasonable prospect for the treatment by genetic engineering of the common diseases of multifactorial - complex genetic and environmental - causation. As far as we know, large numbers of unidentified genes determine susceptibility to these diseases and, if it is not yet possible to correct a single gene defect in man, there can be no reasonable expectation of correcting a polygenic predisposition. Equally, it is not feasible to contemplate a "eugenic" program to eliminate these common diseases.

Nevertheless, the ultimate control of these diseases is feasible and here I believe that medical geneticists should play a leading part. It should be a major commitment of medical geneticists, by family studies and other techniques, to identify those members of the community who are genetically predisposed to these diseases. Then efforts could be made to identify and to remove the exogenous factors which are responsible for the expression of these diseases in the genetically susceptible. The removal or modification of environmental pathogens is feasible;

the alteration of a polygenic predisposition is not.

This program may not be as dramatic or as exotic as genetic engineering but it is the most effective approach now available to the ultimate control of these common diseases in our communities. I am not proposing a reduction of support for research in molecular biology; rather I am suggesting that a great deal more support from public and private sources and a greater involvement of research workers should be made available for this potentially more effective approach to the improvement of the quality of human life.

The Genetic Approach to Peaceful Co-existence

I began my presentation by suggesting that the beginning of genetics was the beginning of civilization, not its fulfillment. After 10,000 years, much as been achieved in the art of classical Greece and the Renaissance, in the music of the Baroque and the Romance, in the writings of innumerable theologians, philosophers and storytellers, in the physico-chemical analyses of the structure of living and inanimate things, and in the applied technology of skyscrapers, supermarkets and space travel. This much has been accomplished but we have by no means achieved an acceptable degree of civilization. There is still violence in our cities and wars between our nations. We have not yet mastered the fundamental criterion of civilization, which is the ability for men to live together harmoniously in our communities, in our cities, in our countries, and in our world.

Human antagonism, whether overtly economical, political, religious or racial in character, has its roots in most peoples' ignorance of the biological basis of human differences. High up on my list of priorities for human geneticists is

the promotion of a more general understanding of why people differ in their physical appearances, in their habits, in their beliefs and in their ambitions. The geneticist analyzes population groups statistically in terms of their gene frequencies and can show that, genetically speaking, the affinities of all mankind are much greater than the superficially observed differences between peoples.

Perhaps when this unemotional, statistically objective way of thinking becomes common practice, men will have a better understanding of their relationship to their fellow men. The futility of national and racial pretensions to superiority and domination will become apparent and men will concentrate on developing their inherent affinities for the good of all.

Then we can look forward to a true state of civilization in which all our energies can be directed towards the positive promotion and the universal enjoyment of a continually improving quality of human life.

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Table 1

FORBIDDEN MATINGS (Leviticus 18.6-18)

GENETIC	SOCIAL
mother	step-mother
daughter	step-daughter
sister	fraternal sister-in-law
half-sister	
granddaughter	step-granddaughter
aunt	paternal aunt by marriage wife's sister, while wife is still alive

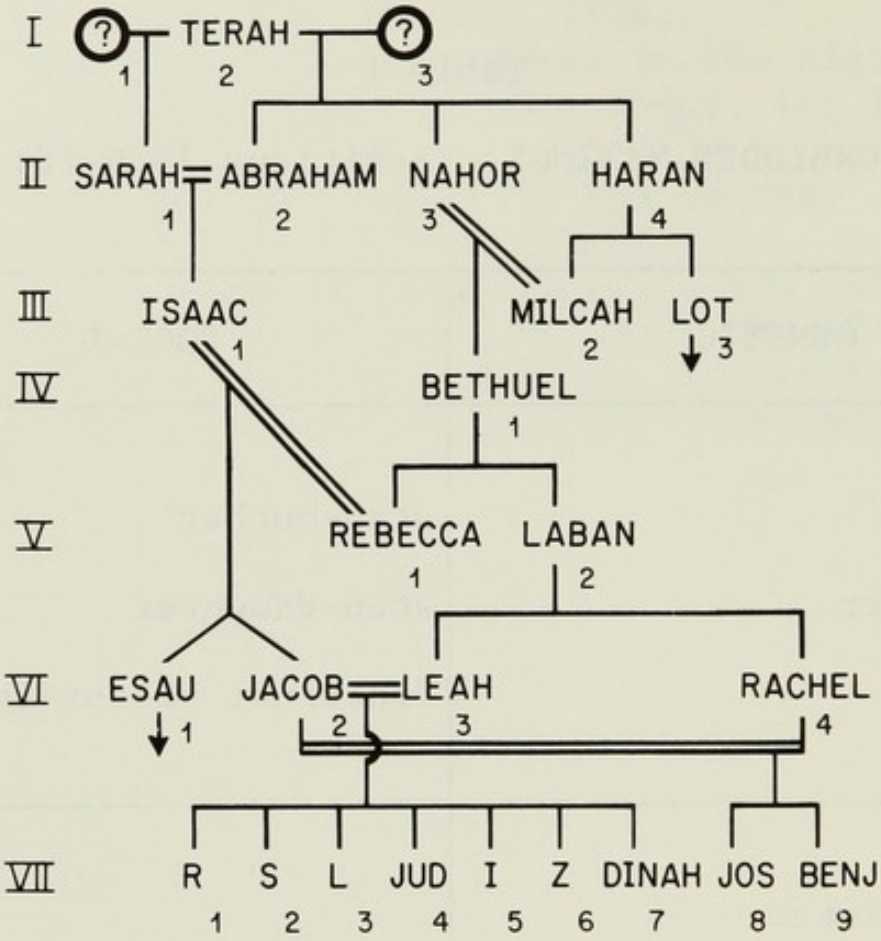

Figure 1. The Pedigree of the Patriarchs. The names of Terah's two wives (I.1 and I.3) are not known. In generation VII, the abbreviations refer to the 9 children of Jacob by Leah and Rachel: Reuben, Simon, Levi, Judah, Issachar, Zebulon, Dinah, Joseph and Genjamin. The arrows below the names of Lot (III.3) and Esau (VI.1) indicate that they had decendents who are not considered here.

DISCUSSION

DR. PORTER: Is there any evidence that the change from a nomadic to an agricultural mode of life introduced new diseases? For example, it is postulated that sickle cell anemia became prevalent in Rome after the introduction of iron tools.

DR. GORDON: No, there is no evidence since there are no written records. The skeletal remains do show far more frequently things like bone fractures and certain inflammations. It is curious that in those skulls that have teeth and dental caries, the teeth show a lot of wear from grain eating. This is also evident in the neolythic specimens which are available for study. There is nothing to tell us about the types of modern diseases. We have to wait for Egyptian mummies, which come about 5000 years later, before we can see the ravages of infection, but not in the neolythic remains. When I said this was a great improvement in health, I only inferred this indirectly because, clearly, this community grew rapidly. Nevertheless, those skeletal remains that exist are usually of comparatively young people. There are no skeletons of old people from the neolythic period, but I must emphasize that the human remains are extremely scant and those that have been found have not yet been adequately studied.

DR. MOTULSKY: Dr. Gordon, would you not expect that the in-breeding, such as that seen in the Ashkenazi communities of eastern Europe, would, in fact, not explain the incidence of genes for recessive disorders in this population but, in fact, tend to diminish it?

DR. GORDON: Dr. Motulsky, you know the answers to these questions better than I. On the other hand one might argue that the carrier state, the heterozygote, had certain advantages. For example, on quite inadequate evidence it has been argued that the high frequency of familial dysantonomia in Jewish communities occurs because the heterozygotes are more intelligent. I do believe, however, that as a result of religious isolation and social pressures on a religiously isolated community, there is probably a great deal of inbreeding. It is unlikely, however, that first cousin marriages were more frequent than in communities outside the isolate but I think people were probably more closely related than they realized. Quite recently, I saw a Dutch family living in a small isolated community in northern Minnesota in which there were three children with dysantonomia. On taking a routine family history there was no consanguinity but as we started tracing the family back further, we were able to demonstrate to the parents of the patients that they were, in fact, second cousins although they had not realized it. The result of communal living does, because of social and religious pressures, lead to a certain amount of inbreeding and certainly it is a fact of genetic life that in these small inbred communities there is a great deal of autosomal recessive disease. One goes to these communities to find these diseases. On the one hand, the heterozygote may be surviving because he has some advantage, a theory that has been demonstrated in only a couple of instances and, on the other hand, the consanguinity is such that although the patients are dying out, there are not that many of them to produce an observed effect over this period of o one or two thousand years.

DR. PORTER: Investigations done in Israel comparing Sephardu and Ashkenazic Jews show remarkably little divergency in polymorphisms considering that they had been separated for about two thousand years. Did this not surprise you initially? I believe glucose-6-phosphate dehydrogenase deficiency is an exception.

DR. MOTULSKY: No, but that ties in with the argument you were making with Dr. Gordon and that is why I brought up that particular point.

DR. GORDON: I think it is perfectly in keeping with the data. Amongst the Jewish communities, the resemblances of such things as frequency of the various haptoglobin phenotypes and Rhesus negativity are remarkably similar. You quoted one exception, glucose-6-phosphate dehydrogenase deficiency, which is fairly easily explained. This occurred in the oriental communities and those who settled in the territories which are now Iran and Iraq in the malarious areas and even within those oriental communities there are isolates with considerable amounts of glucose-6-phosphate dehydrogenase deficiency. I think you've taken the one example where there is a fairly reasonable explanation. But I think it is quite remarkable that these Jewish communities, members of which have been separated for two thousand five hundred years, still resemble each other in Rh negative and Hp-1 frequency.

You've got to be quite careful in attributing a genetic basis for morphological differences. I used to amuse myself when I visited Jericho, by putting on an Arab headdress and I passed as a very good Arab! It is astonishing what local color does. But I accept that there obviously must have been outbreeding as well. Pigmental changes, for example, would suggest this. On the

other hand, despite the superficial morphological differences, when one gets down to the measurable and analyzable genetic traits, I am, like Dr. Porter, surprised at the similarity rather than at the dissimilarity.

DR. CHASE: I don't know why you should be so surprised. We have the example of the American Indians where there is even a longer period in which they were separated from their ancestors.

DR. GORDON: I agree with that example entirely and, in fact, it also includes what Dr. Motulsky might regard as an exception. Blood group B, which perhaps has its highest frequency among the Mongolian people in far eastern Asia, is extremely low in the North American Indian and particularly in the Eskimo group. I don't know the explanation. I think this is one of those kinds of exceptions which is intriguing but your argument is correct. In all other characteristics which have been measured, the American Indian and the Eskimo closely resemble Mongolian forebearers and there have been nice examples of blood group B which allows for all sorts of speculations.

RONALD G. DAVIDSON (State University of New York at Buffalo, Buffalo, New York): Again, I agree with this, except that I would hate to see the administration decide that there would be an all out war against cancer instead of providing additional funds to fight this problem. It appears as if we were going to have funds that were designated for other areas now diverted to cancer research, and other programs begin to suffer. At the turn of the century, the medical world laughed at Garrod for studying a group of exquisitely rare diseases. Harvey realized, and

most scientists today realize, that it's through studying rare diseases that one has been able to obtain answers to some very complex problems.

DR. GORDON: You start off as though you were going to take issue with me but I don't think we are at odds. I certainly would not like to see any reduction of funds for basic research. I've always been a firm believer in the intellectual as well as the applied aspects. I believe that science would be dry, dessicated, uninteresting and, indeed, unimportant otherwise. The implication that I was making was really the one you were making: namely, that there is a disproportionate amount of money being spent on research in rare diseases. Quite recently, in a conference in Washington, I was surprised to find that there is one group funded by the National Institutes of Health at the moment which is concerned with the studies of the genetics of ischemic heart disease, whereas there are several groups studying metachromatic leukodystrophy, of which there are some 30 known cases in the literature. This is the kind of thing I was getting at. I am also concerned about the fact that the glamour and excitement - and I am excited by it - if molecular biology is attracting far too many scientists from more mundane matters. Now, again, this has as many scientists as you wish doing molecular biology. I thoroughly enjoy reading about it and find it intellectually stimulating. But, if within the next twenty years we want to see some achievements in the more widespread health problems, then a greater amount of attention must be paid to common diseases. I agree, let's not take anything from anybody, but let's give more to the study of the common diseases.

ONGOING HUMAN EVOLUTION

Albert Damon

This paper will discuss ongoing human evolution with particular attention to a situation where some of its aspects are occurring before our eyes: the transition in societies defined as "primitive" by the World Health Organization[1] from traditional ways of life to the larger, cosmopolitan culture. It took some 500,000 years and 25,000 generations for man to evolve from Homo erectus to Homo sapiens, with a steady improvement in tools and other aspects of culture over the whole period. It has taken Homo sapiens tens of thousands of years, and many hundreds of generations, to proceed from hunting and gathering to shifting agriculture or pastoralism, then to settled agriculture and, in the last hundred years, to industrialization and urbanization. Today, on all continents, we see people raised in traditional societies suddenly, on a massive scale, being introduced to the complexities of modern life. This is particularly striking in New Guinea, where stone-age hunters or agriculturists settle in Port Moresby, a modern city with air-conditioned skyscrapers and traffic jams. But even those who remain in their villages encounter Western technology in the form of tools, food, medical care, and cash cropping. The effects of this rapid acculturation are scientifically instructive as well as directly relevant, in a practical way, to the continuing

evolution of man.

My discussion will be organized in four sections: where mankind is, biologically speaking; how we got here; where we are going; and, finally, some biological aspects of the transition from primitive to civilized ways of life. I shall illustrate various points from my own research among primitive populations, both in the Solomon Islands and in Cambridge, Massachusetts.

I. WHERE MAN IS, BIOLOGICALLY SPEAKING

Man is the most successful of all animal species. We dominate all other animals. In sheer bulk of biomass, we are the largest single species on earth - that is, the average weight per person multiplied by the number of people. The numbers of mankind continue to increase too fast to permit any kind of balance with ourselves or with other animals, let alone with the natural resources on which all life depends. We are the most widely dispersed species, occupying a great variety of climates, altitudes, and habitats. Homo sapiens consist of a single species which interbreeds readily, even though it has been fragmented into many geographic subspecies or races. Races can be defined as breeding populations. They are distinguished not only physically, but also by physiological and biochemical characteristics, as well as by distinctive patterns of disease susceptibility and resistance.

Without discussing in detail all the biological characteristics of man, I shall merely list a few. As a mammal, man has internal temperature control, immunologic specificity, a well-developed central nervous sustem, differentiated teeth, seven cervical vertebrae and a four-

chambered heart. Mammals alone have hair or fur, sweat glands, a uterus, a placenta and suckle their young. Mammals develop slowly, in family groups, and have refined play and sleep to fine arts. Among the mammals, the primates have specialized for living in trees. They developed nails instead of claws, versatile hands, and clavicles which free the arms from the body. They have binocular color vision. Their outstanding attribute is a large cerebral cortex. Primates have lost a few biochemical capabilities that other mammals retain, notably the ability to synthesize Vitamin C. In addition, the great apes and man cannot break down uric acid via the enzyme uricase. It is hard to see what advantage has been gained by these biochemical deletions.

Among the primates, man is distinctive for his upright posture, opposable thumb, large brain, speech, and above all, culture. Human sexual activity is year-round, rather than episodic, which has had a profound effect on his social life and organization.

II. HOW WE GOT HERE: THE PROCESS OF EVOLUTION

Mankind reached its present state by the same biological path followed by all species - that is, the evolutionary process. Evolution works by selection acting on a store of heritable variation. The heritable variation is provided by the mutation of genes and chromosomes. Selection influences fertility and mortality, that is, birth or death rates, to preserve good traits and to eliminate bad ones. Good and bad are defined in terms of adaptation to the particular environment of a population at a particular time. The fit survive: the more survivors they leave the fitter they are. Fitness in the strict Darwinian

sense is defined solely in terms of the number of offspring surviving to reproductive age. Fitness has nothing to do with health, intelligence, value to society, or accomplishment of any kind other than reproductive. From the standpoint of biological evolution, a moron with 14 grown children is far more fit than Leonardo da Vinci, who had none.

At this point, let us consider two further evolutionary principles, sometimes overlooked. First, selection works on phenotypes, though only genotypes constitute heritable variation. This means that selection always judges the book by its covers. A brilliant gene or genotype will be lost unless it appears in a person who will survive, reproduce, and care for his child until the child can reproduce. For example, albinos in the tropics, however gifted, do not as a rule survive, although there are exceptions. Even persons with a trivial but unesthetic condition like tinea impricata may never marry and reproduce, however gifted he may be.

The second principle is that polygenes are far more important in human evolution than the single genes of classic Mendelian genetics or Garrod's "inborn errors of metabolism". The criterion of importance again, is quantitative. The sum total of death, disability, and economic loss due to single-gene diseases is a tiny fraction of that due to the diseases of multiple causation, which are the polygenic diseases with a strong environmental component. Heart disease, strokes, cancer, diabetes, and arthritis are just a few examples. And even in the area of normal function, quite apart from disease, such major characteristics as size, shape, strength, speed, skill, skin color, and various mental abilities are all polygenic.

The mechanisms of evolution are four: mutation,

selection, gene flow, and drift. Mutation rates, while differing from one gene to another, are fairly constant for each gene under natural conditions, averaging around 1 per 50 to 100,000 or so in all populations. It is doubtful whether mutation rates can be slowed, but they can be accelerated by heat, radiation, and certain chemicals. Artificial mutagens therefore constitute a hazard to man's genetic future. They have not been important in the past.

Gene flow, or migration, and random genetic drift, are opposite in effect. They have always taken place in human evolution. Gene flow from one population to another kept Homo sapiens a single, interbreeding species. On the other hand relative breeding isolation, whether geographic or cultural, has resulted in a variety of adaptations to particular environments. This is the origin of the different subspecies or races of man. Among the small bands which constituted the breeding milieu for 99% of human life on this planet, Gajdusek[2] has emphasized the genetic impact of chance in the form of random drift, founder effects, accidental loss of certain genes, and gain of others, as from capture or shipwreck. He believes that chance rather than selection accounts for much of the genetic variation among breeding isolates. Of course, we are also seeing the end results of past selective crises[3] none of which we can reconstruct, but whose presence we can infer from Harris'[4] observation that about 30% of all loci are polymorphic. The blood groups are a good example; their selective advantage remains obscure, despite suggestions that they may confer immunity to infections like smallpox and plague. We cannot conclude that selection is unimportant merely because we cannot see it operating at the moment. We know from the story of myxomatosis in Austral-

ian rabbits,[5] and from the halved frequency of sickle-hemoglobin genes in New World Negroes since they arrived from Africa, that strong selection or relaxation of selection can alter gene frequencies greatly in surprisingly few generations.

Selection in man is both natural and artificial. Factors in the environment to which man adapts by natural selection include disease, food supply, and physical features of the habitat, such as climate, altitude, and light. Biochemical and physical adaptations to these environmental factors characterize the descendants of populations long resident in distinctive habitats.

Artificial selection includes selective mating and sexual selection. Selective mating occurs when some characteristic is prized, and persons of either sex possessing it are therefore at a reproductive advantage. Health has always been desirable; so has physical vigor, strength, skill, smooth skin, and harmonious physical development. Intelligence is now thought to be such a characteristic in the modern world. Selective mating for intelligence could explain the several-point increase in I.Q. among Scottish children between 1932 and 1947. To take another example, skin color: in Japan and India, light skin color is prized in mates of either sex.[6] Among the isolated Wagab of the New Guinea Highlands, dark-skinned persons are preferred.[7] To the extent that such traits have a genetic basis, they will increase in populations that practice selective mating. Both gene frequency and genotype frequency will change.

In sexual selection, certain traits are prized in one or the other sex. Darwin believed that man's smooth, hairless skin results from sexual selection of females for hairlessness, since it

has no apparent advantage otherwise. The same is probably true of breast development in women, since among the primates, including the great apes, even lactating females have breasts little or no larger than those of males. Most human breast tissue is, in fact, fat rather than functioning glandular elements. Perhaps the most spectacular example of human sexual selection is steatopygia, the deposition of fat on the female buttocks among Bushmen, Hottentots, and Anadaman Islanders, serving no apparent function other than decorative.

In the United States, tallness in men seems to be another such characteristic, much more so than in other societies. In a series of 2,500 Harvard men whom we followed for many years after college, those that had children were taller than those that did not. A generation ago, the folk saying was that "gentlemen prefer blondes", but one doesn't hear it much these days. Perhaps the gentlemen have disappeared; the blondes seem to be doing fine.

Except for intelligence, it is unlikely that selective mating or sexual selection will have more than a minor, locally variable effect on future human evolution. The ideals sought in mates vary too much from time to time and from group to group.

Another form of artificial selection is selective breeding, by design rather than choice. Selective breeding would include prescribed marriages, as among royalty or Indian castes, who have hereditary skills shich may rest partly on a genetic substrate. Wars, conquests, slavery, and other social institutions alter "natural" breeding patterns markedly. The ancient Chinese held competitive examinations, in which brilliant boys could enter or rise in the ruling class, marry the daughters of high officials, and pass

on their genes. Other societies which provide social mobility via their educational, religious, or military systems do the same. On the other hand, religions which impose priestly celibacy have the opposite effect, losing a portion of their superior genes in every generation.

Changes in man-made environment since the invention of agriculture and domestication of animals have imposed new conditions for selection both natural and artificial. Crowding increases the spread of infectious microorganisms and parasites, to which populations have had to adapt. Marked population differences in susceptibility to disease reflect previous exposure, not only during individual's life times, but also in the population's past history. The most striking examples are the world-wide decimation of previously unexposed populations by tuberculosis, smallpox and even measles.

Modern cities which combine crowding, overstimulation, and disruption of normal biological cycles, are another new environment.

Further man-made changes in gene frequency result from medical advances, which permit the survival and reproduction of those who would otherwise succumb to genetic diseases like diabetes, cystic fibrosis, phenylketonuria, or sickle cell disease. Medical progress sweeps many genetic diseases under the rug, as it were, creating a sizeable genetic load dependent upon a stable social order.

Social policy, in the form of taxation, welfare, and birth control, can have a profound effect on birth rates, just as medical and public health measures affect death rates. To the extent that the persons affected differ genetically, gene frequencies in the population will change.

Relaxed selection means that the force of

selection for or against certain genes no longer holds in new environments. Sickle hemoglobin, no longer an advantage in the absence of malaria, is decreasing in frequency. Under the opposite kind of selection, a gene which is no longer harmful may increase in the new environment. Many "primitive" people have very little or no color-blindness, near-sightedness, or astigmatism. They have greater ability to taste phenylthio-carbamide and other substances. Industrialized populations in Europe, America, and Japan have much worse eyesight, and some are poorer tasters, than those living in simpler societies.[9,10] Deformities of the nasal bones and cartilege are likewise more frequent in industrialized than in simple populations.[11] Conceivably the thinner skull of modern man reflects relaxed selection to withstand blows on the head.

The final mechanism of selection I shall mention is the reduced scope for natural selection brought about by lowered birth and death rates in advanced countries. We have now reached the point where most people survive and reproduce small families, so that both birth selection and death selection have a much smaller range of variation than formerly. The opportunity for selection depends on variability in birth and death rates. For fertility, as an example, the opportunity for selection is measured by Crow's index, $S.D.^2/m^2$, where S.D. represents the standard deviation and m the mean of the number of children born to a population.

On the other hand, this reduced variance affects only those zygotes (fertilized ova) that reproduce. Penrose[12] estimated that close to half of all zygotes never reproduce. About 15% are lost before birth, 3% are stillborn, 2% die shortly after birth, 3% die before maturity, 20%

never marry, and 10% of those who marry remain childless. Thus, there is still considerable scope for selection. Genotypic differences that favor survival to reproduction at any of these stages will enjoy an advantage.

Selection: end results. We have now discussed five types of selection - natural, sexual, artificial, relaxed, and reduced selection. Under artificial selection we considered selective breeding and the man-made environment. Let us now look at the end results of selection. There are three main types, directional, stabilizing, and disruptive.

1) Directional selection occurs when one gene, one combination, or one end of the normal curve of distribution for polygenes has selective value, that is, is favored in survival and reproduction. When an environment changes, adaptation to the previous environment may become maladaptive. The species will then evolve in such a direction as to adapt to the new environment. Examples of directional selection in man are long-term physical changes like those toward earlier maturation, increased body size, roundness of head, increased head size, thinning of skull, loss of third molar teeth, more speculatively, increased intelligence, tolerance of crowding, and resistance to certain infectious diseases associated with crowding - tuberculosis, for example, may represent directional selection.

2) There are also current examples of stabilizing selection. Stabilizing or normalizing selection maintains a currently successful adaptation. This is the force that ensures the present successful and characteristic phenotype of a species, while preserving its variability, since by definition most individuals fall around the mid-region of the normal curve of distribution and are heterozyzous for polygenes. One

kind of selection, for the individual rather than the species, is longevity. I have been following[13] a cohort of 2,600 men who were measured at Harvard between 1880 and 1912, and over 95% of whom have now died. The men of average height and weight in college lived longer than the very tall, the very heavy, the very short, or the very light. This is stabilizing selection.

As regards the number of children of those men in the group who had married, representing selection at the species level - once again, men of average height had more children than the very short or very tall. The same relationship held among 2,300 middle-aged factory workers in Chicago, 700 veterans in Boston, and 189 tribesmen in the Solomon Islands. In the medical literature, confirmation appeared in three unlikely sources. Newborn children of average birth weight had a considerably lower mortality rate than the very light or the very heavy.[14] Among 6,200 Polish Army recruits, the number of living sibs, and hence family size, was greatest in men of average head form, falling off in both the long-headed and broad-headed.[15] And finally, among 23,000 persons discharged from 1200 hospitals in this country during 1969, patients whose weights were near the national average for their age and height had shorter hospital stays, by 2 or 3 days, than those considerably underweight or overweight.[16] So in respect to length of life, number of children, and duration of hospital stay, the man of average physique is better off than the extremes. This is stabilizing selection.

3) Disruptive selection is not evident at present and is highly unlikely to occur in man's future. Earlier, geographic isolation facilitated the evolution of Homo erectus from his

australopithecine forbears, and the subsequent evolution of Homo erectus into Homo sapiens. But in a few years the last remaining isolates of Homo sapiens will be brought into the mainstream, which is itself rapidly becoming homogenized around the world.

We have now covered the biological process of evolution. Man has added something new to the evolutionary picture - namely, culture, a distinctive human attribute. Culture provides the mechanism for adaptation, in the form of communication, technology and social rules and regulations. The technological aspect of culture has also created an entirely new environment, a man-made world, which has become more important than the natural environment as the setting for human evolution. We are now being selected for adaptation to this new environment. It is artificial in the sense of being man-made, but one could argue that the natural habitat of Western man is precisely the crowded, polluted, noisy city with its factories and highways, its packaged food, drugstores, hospitals, and television.[17]

III. WHERE WE ARE HEADING, BIOLOGICALLY

Now that we know who we are, biologically speaking, where we are, and how we got here, let us see where we are heading. Certain general trends can be noted. First, man is enormously mobile. One of the striking characteristics of modern life is the continuous, rapid movement of large numbers of people daily, ranging from the commuter ebb and flow to the jet planes which make all places on the earth only a few hours apart. Starting with small bands who walked, sailed, and paddled from their original homes in Africa and Asia, man has colonized most of the

world. Domestication of animals speeded up the process. The horse and camel transported thousands of Asiatics westward to Europe. Boats dispersed millions of Europeans to the Western Hemisphere and to Australia, where they displaced, sometimes eliminated, but always mated with the original inhabitants. Large numbers of Africans were brought to the New World. The end result has been gene flow on a massive scale, the enormous increase of some human stocks and the decrease of others. Technology, in the form of agriculture and public health, continues to permit great population increase in Africa, Asia, and Latin America, while the populations of the developed countries are becoming stabilized, due to technical advances in birth control.

A second general trend, already mentioned, is the homogenizing of the world-wide environment. Along with mixing of genes has come an increased uniformity of our surroundings. Temperature and humidity control make it possible for men to live and work comfortably in any part of the world. Cities on all continents have common problems of noise, crowding, pollution, and traffic jams. Urbanization and industrialization form the environmental backdrop for increasing numbers of people all over the world.

For a third major trend, genetic mixture is increasing, though the vast majority of mankind still mates within narrow geographic, linguistic, ethnic, and tribal limits. Hybridization of breeding populations which had been isolated for hundreds or thousands of years could theoretically result in heterosis, or hybrid vigor. It means an increase in size, health, and fertility, probably as a result of masking harmful recessive genes by dominant alleles at many loci. Heterosis has also been ascribed to epistasis, or the effect of new gene combinations, over and above

the specific action of those genes individually. The evidence for heterosis in man is, however, inconclusive,[18] as will be shown shortly.

Before discussing at some length two more major trends in ongoing evolution, increased body size and earlier maturation, let me list, by way of recapitulation, some of the features mentioned so far: the population explosion, birth control, industrialization, urbanization and the breakdown of breeding isolates. Technical and medical advances increase longevity, keep defective persons alive, sometimes to reproductive age, and shift the spectrum of disease from the infectious and malnutrition to the chronic degenerative, noninfectious diseases like atherosclerosis, hypertension, cancer and stroke. Civilized man exercises less than primitive man, eats more, and grows obese. He is increasing his exposure to mutagens, and he is probably being selected for intelligence and for tolerance to crowding, competition, noise, and the other aspects of urban life.

We come now to the secular (long-term) trends in body size and age at menarche.

For at least the past 100 years, and probably longer than that, people have been getting bigger, and also getting bigger earlier.[19] This increased adult size has been noted in Europe, the United States, and Japan. In addition, there has been a dramatic decline in the age at menarche, or first menstruation. Adult height has increased at the rate of 1 inch per generation of 30-odd years, so that men are now 3 inches taller than men in the 1960's. Moreover, men now reach their adult height in their very early 20's, instead of in their very late 20's, as they did 100 years ago. The age at menarch, or first menstrual period, has advanced one year per generation, so that the mean age now in

developed countries is between 12 and 13 years of age. This is about 3 years earlier than it was 100 years ago. This secular trend toward earlier maturation has been called[20] "one of the most considerable phenomena of human biology, with a host of medical, educational, and sociological effects". Let's look at some examples.

Among fathers and sons at Harvard between 1880 and 1920, Bowles[21] found that the sons measured 1.3 inches taller than their fathers on entry to college, although the sons were a year younger. between 1920 and 1946, American soldiers in the Second World War were 0.7 inches taller than those in the First World War. Since 1946, there has been a further increase of 0.5 inches, making a total gain in height of 2.5 inches among U.S. men between 1880 and the present time. If this trend continues, we may produce a nation of basketball players, but fortunately the end is in sight. In fact, in a paper with precisely this optimistic title, "Increase in Stature. Is the End in Sight?", Bakwin and McLaughlin[22] compared Harvard freshmen admitted in the 1930's with those admitted in 1958 and 1959. Boys from public schools were continuing to increase in height, whereas those from private schools were not. The implication was that the environmental conditions influencing growth, such as nutrition and medical care, were still improving for the public-school boy, but had earlier reached optimum for the private-school boys and had remained constant.

My own work[23] on Harvard men measured between 1870 and 1965 confirms this possibility. Among 12 families in which 4 generations had been measured at Harvard - father, sons, grandsons and great-grandsons, 85 men in all, most of the height increase occurred between the fathers and sons (born 1858 to 1888), a minor portion between sons

and grandsons (born 1888 to 1918), and practically none thereafter among men born between 1918 and 1941. Further unpublished data of mine on 6,000 men in 2- and 3-generation Harvard families show the same result. Again, the implication is that these favored families reached an optimum environment in the decade 1910-1919, so that genetic determinants of height could reach their full expression early in this century. For families less well off, the environment is still improving and with it the chance for full expression of the genetic determinants of height.

Evidence that the secular increase in body size is slowing down comes from two more studies, Froehlich's[24] among Japanese immigrants to Hawaii and my own[25] among mothers and daughters attending Mt. Holyoke and Wellesley Colleges.

Explanation. How can we account for the long-range increase in adult body size? Two general kinds of explanation have been advanced: the environmental, which is certainly true, and the genetic one of heterosis, or hybrid vigor, which may possibly be true as well. Needless to say, these two explanations, environmental and genetic, are not mutually exclusive, both factors can be operating. Clearly, major changes in physique within a single group over one or two generations, as among the Japanese in Hawaii, can only be environmental. The same reasoning applies, incidentally, to the epidemic increase in certain diseases in this country during the present century, such as coronary heart disease, peptic ulcer, and lung cancer. Genetic influences, by and large, simply don't operate that rapidly; they usually take many generations. But there is one kind of genetic influence that could act within a single generation for a given group, and for several generations in a large national population. That influence is heterosis, well known

to plant and animal breeders. When two inbred strains are crossed, the F_1 offspring are larger, healthier, and more fertile than either parental stock. Now the relation of size to fitness is questionable. Fitness, strictly speaking, refers to the number of offspring reaching reproductive age. Nevertheless, the fact remains that increased body size does, on the whole, accompany fitness in the strict sense, in plants, animals, and possibly man. Dahlberg, a Swedish geneticist, was the first to propose, in 1942, that heterosis might account for some of the secular increase in height. The theory is that increasing social and geographic mobility breaks down breeding isolates, a process that presumably accelerated with the invention of the bicycle.

Evidence for the environmental factor in stature is overwhelming. The Harvard fathers and sons are a good example: keeping heredity more or less constant, their stature increase over time reflects environmental change. To take another example, I have studied 200 second-generation Italian-American workers in a single factory near Boston, all born and raised in the United States by parents who were themselves born near Naples, Italy.[18] Within this homogeneous group, there was a steady increase in height as one compared men in their 50's with those in their 40's, 30's, and 20's. The total amount of height gained over three decades was 2.1 inches. So large an increase over so short a period within a single group can only be environmental. The two specific factors in the environment that are mainly responsible are better nutrition and prevention or control of the diseases, chiefly infectious, that could retard growth in childhood. After the long bones stop growing, very little growth is possible, mainly in the spine, so that adult malnutrition or disease will have a neglible effect

on growth.

There is some slight evidence that heterosis may occur in human populations. Hulse[26] compared the height of Swiss migrants to California, their children born in California, and villagers who remained in Switzerland. The total height increase in the California-born men over the Swiss who remained at home, was 1.5 inches. Of this amount, 1 inch was due to the California environment and 0.5 inch to the fact that these men were more likely than those who remained in Switzerland to have had parents from different Swiss villages. Actually, no heterosis due to exogamy was demonstrable among the sedentes or the migrants! Among the Italian-American factory workers,[18] men whose parents came from different villages averaged 0.75 inch taller than those whose parents were from the same village. Both of these sets of positive results are at borderline levels of statistical significance.

There is also evidence, from inbred regions of France[27] and from the Hutterite religious isolate[28] that inbreeding in man is associated with short stature - a roundabout way of suggesting that outbreeding or hybridization, should be associated with tall stature. The trouble is, when one examines large populations of widely differing groups that have crossed, such as Caucasians with Chinese or Japanese in Hawaii, and when one examines such direct aspects of hybrid vigor as rates of stillbirth and neonatal mortality, one finds no evidence of heterosis.[29] Even in stature, most descendants of racial crossing on a large scale are intermediate between the two parent stocks, rather than being taller than either one.[30] We must conclude then that the case for heterosis is unproved. It remains just a possibility, pending further research.

Let us now turn to the second aspect of the

secular trend, earlier maturation. Soldiers in the Civil War continued to grow into their late 20's; nowadays, male growth is virtually complete by age 22, and female growth by age 18. At all ages, children are now larger than they were even one generation ago; the amount of this difference, of course, decreases the closer boys get to age 22 and girls to age 18. But several lines of evidence show that the speeding up of growth is not enough by itself to explain the increase in adult body size; the two phenomena are distinct.

The most dramatic evidence of the speedup in maturation is the age at menarche, or first menstruation. Progressive lowering of the age at menarch has occurred in the United States and Western Europe for at least the past hundred years, and in Eastern Europe since the late nineteenth century. The amount of acceleration has been between three and four months per decade or roughly one year per generation, so that the age at menarche is now about 3 years earlier than it was a century ago.[19] In general, city girls have menarche earlier than country girls; the well-to-do, earlier than the poor; and American girls earlier than their contemporaries abroad. Among immigrants to America from Europe and Japan, the first generation of girls born in the United States had earlier menarche than their relatives who remained behind.

The best way to measure the acceleration would be to observe the age at menarche of successive generations within families, just as height and weight were observed within the Harvard families. This was done[31] for 66 mothers and 78 daughters, the daughters being subjects in a longitudinal study of child growth conducted at the Harvard School of Public Health between 1930 and 1956. On the average, the mothers were born in 1907, and their daughters in 1934. There was a

striking acceleration of 1.5 years between mothers' and daughters' age at menarche, from 14.4 to 12.9 years. This was not due to a few very early maturers among the daughters; their whole distribution was moved up.

What can account for a difference of this magnitude in a single generation? Since the genetic factor was held more or less constant by comparing mothers and daughters, genetics cannot account for the acceleration. Age at menarche does have a genetic component; twins, sisters, and mothers and daughters are more alike in age at menarche than unrelated women. But clearly in the present case, we must look to the environment.

Since the mothers were recruited from a hospital clinic, their socioeconomic scale, as judged by comparing education of mothers and daughters, and education and occupation of the corresponding sets of husbands. But what specific factors in their environment could be responsible for their earlier menarche? Nutrition is the best-established influence on rate of maturation. The amount of its effect is uncertain. The best estimate in the United States is based on white girls in Alabama, where the mean difference in age at menarche between undernourished rural girls and well-nourished city girls was 2/3 of a year.

In the Harvard Study, the daughters did have a better diet than the mothers, but the mothers were never as poorly nourished as the Alabama girls. Even if we assume the extreme case - that the mothers as a group were as undernourished as the poor Alabama girls - nutrition would account for only 0.66 years, of the 1.5 year advance in age at menarche from mother to daughter. What can account for the remaining 0.8 years?

Medical advances could accelerate menarche by preventing disease. The evidence is, however,

that most childhood diseases are totally without effect on the growth of well-nourished children.[32,33] Persistent chronic disease among malnourished children could indeed retard menarche, but this combination had not occurred among the mothers to any significant extent.

Psychosocial influences. We are left with a large fraction of the secular advance in age at menarche to explain. The psychosocial factor is poorly understood and has been disputed.

We have seen that urban girls begin menstruation earlier than rural girls - and urbanization is one feature of the environment that has increased steadily since the secular trend in age at menarche has been observed. Rural girls as well as urban girls show the secular advance. If so, "urbanization" might be interpreted as some unidentified aspect of the environment which is greater in the city than in the country, and which has been increasing over time in both city and country. In fact, in countries like England and Holland, where there is now little differences between rural and urban ways of life, there is very little difference between the ages at menarche of rural and urban girls.

What are the effects of city life? Urbanization increases crowding and all kinds of stimulation - sensory, social, and intellectual. Urbanization increases competition and "stress", while decreasing physical exertion. Another factor, coeducation, has also been increasing with time, but has been shown (in Sweden) not to affect age at menarche.

We might speculate that the effect of "urbanization" on age at menarche is comparable to the changes in wild rats brought about by domestication in the laboratory environment.[34] Among other differences, sex glands develop earlier in the laboratory rat than in the wild rat. In

recent laboratory experiments on the age of first ovulation in mice, Vandenbergh et al,[35] attributed 47.3% of the total variance to psychosocial factors (the male presence), and only 4.8% to dietary protein. Body weight, an hypothesized determinant of human menarche,[36] had no influence on the onset of ovulation in mice. Incidentally, Vandenbergh et al,[35] confirmed our own finding[31] that physical growth and sexual maturation are separate processes.

In short, better nutrition, improved health and some as yet unidentified aspects of the material and psychosocial environment are all at work to accelerate the age of menarch.

Like the secular increase in height, the acceleration in age at menarche has slowed down among the well-to-do. Among 500 mothers and their 522 daughters entering Mt. Holyoke and Wellesley Colleges between 1930 and 1970, reported age at menarche was identical, 13.1 years for mothers and daughters.[25]

Whatever its explanation, the secular trend toward earlier maturation is indeed, to repeat Tanner's phrase,[20] "one of the most considerable phenomena of human biology at present, (with) a host of medical, educational, and sociological effects". To mention only a few: earlier reproduction, family formation, and divorce; dropouts from school; lowered voting age; and increasing tension among young people who chafe against rules formulated for earlier generations who were less mature physically and physiologically at comparable ages. Whether intellectual and emotional maturity have kept pace is another matter.

At the other end of the female reproductive span, the age at menopause, when the menstrual periods stop, there is some doubt as to whether this has been occurring later in life. Most

authorities one generation ago gave 45 as the average age in this country, but some put it later. All current studies place the time around 50 years of age.[37] Menopause is more difficult to time precisely than menarche since it occurs over a period rather than at a definite time. Whatever the situation for individual women, there has been no rise in births to women over 45 years of age, making it dubious whether the possible retardation in age at menopause has any evolutionary implication for the species.

IV. GENETIC CONSEQUENCES OF THE TRANSITION FROM PRIMITIVE TO CIVILIZED SOCIETY

There are three kinds of biological effects that accompany the transition from traditional to cosmopolitan ways of life: demographic, medical and genetic. They are closely related, as is each with the social or cultural changes which characterize the transition but which cannot be dealt with here in any detail.

1) Demographically, the shape of the population pyramid in primitive people is generally intermediate between the broadbased pyramid of settled agriculturists in underdeveloped regions like Latin America or India, with high birth and death rates, and the tall, narrow pyramid of advanced societies, with low birth and death rates. Primitive populations in the natural state seem to have moderate birth and death rates. Fertility is regulated culturally, by taboos on marriage and on intercourse during lactation and at other times. Abortion and infanticide, while occasionally practiced, are uncommon among primitive man. Except for oceanic atolls like Tikopia, the numbers of primitive man are usually not limited by the amount of available land but by its carrying capacity.

Thomas,[38] in fact, proposes that population size is determined by balancing the universal desire for children against the extra work needed to feed them in a given environment. Once primitive man survives the childhood infections and reaches adult life, remaining life expectancy is closer to that of technologically advanced man than true of life expectancies at birth.

The nutritional state of primitive groups depends on the fertility of their habitat, being good among the African pygmies and Bushmen or Oceanic fishermen, for example, and poor among the Sandawe of Tanzania, the Siriono of Bolivia, and New Guinea Highlanders.

Exposure to the larger culture weakens traditional taboos, whether by direct missionary influence or by observation and imitation. When, in addition, modern medicine, public health, and improved nutrition become available, the combination causes an explosive increase in population. Such has been the experience, for example, of the Tolai in New Britain, a group whose numbers have increased so fast since World War II as to require massive resettlement by the government on formerly empty lands. They have outrun their means of subsistence. This is a very real, though as yet insufficiently appreciated danger to many primitive peoples. Most attention to overpopulation has so far been concentrated on the single-crop, settled agriculturists of underdeveloped countries. But the Samoans, to take another example, have increased some 10-fold during this century with a doubling time (in 1956) of 18 years.

2) Medically, westernization shifts mortality and morbidity from the indigenous infectious and parasitic diseases, sometimes complicated by malnutrition, at first toward newly-introduced infections. The classic examples are the intro-

duction of venereal diseases, smallpox and tuberculosis by Europeans to the New World and Oceania and of leprosy by the Chinese throughout Australasia. In fact, current mortality and morbidity statistics from the Solomon Islands resemble those of the United States in 1900.[39] It is intriguing that accidents rank as high as the third leading cause of death in both the Solomons and the United States today. One might expect that technology would increase the accident toll, but apparently it does not, relative to other conditions.

With increasing acculturation come the beginnings of the chronic, noninfectious conditions that predominate in the developed countries. Burkitt[40] notes several disease complexes characteristic of technologically advanced societies but rare in simpler ones, notably diabetes, obesity, atherosclerosis, dental caries and malocclusion, and his own postulated "lower bowel complex" which includes appendicitis, ulcerative colitis, diverticular disease, polyps, and cancer. Our work in the Solomon Islands may have established an "ocular complex" - astigmatism, myopia, glaucoma, and color-blindness.[10,39] For a fuller treatment of the impact of civilization on human biology and medicine, see Boyden.[41]

3) Genetically, we have already noted some of the ongoing evolutionary trends in modern man, the current into which preliterate societies are being swept. Such trends include the breakdown of breeding isolates, selection for adaptation to new man-made environments and to "new" diseases, relaxed selection against traits no longer harmful, environmental amelioration with consequent full expression of genotypes, and the coexistence of stabilizing with directional selection. Let us now consider a few immediate genetic mechan-

isms and consequences of the transition from primitive to cosmopolitan ways of life.

Neel[42] has drawn attention to the drastic change in selection intensity when fitness, or reproductive success, no longer corresponds to ability. In many primitive groups outstanding men, whether hunters, planners, or artists, have more wives and children than other men. Among the Yanomama, a South American Indian tribe, fewer than 49 of the men contributed 23% of the tribe's grandchildren. Selection intensity, being proportional to the variance of the number of children per person, is very high in the Yanomama. Contrast this with the situation when polygymy is forbidden, customary limitations on reproduction are discarded and most children survive - all of which can occur within one generation after culture contact.

Another intriguing question is the variability of inbred isolates in polygenic traits. Paradoxically, inbreeding should increase variability by increasing homozygotes at the expense of heterozygotes. Neel has, however, found no such increase in metric and morphologic traits among Brazilian Indians, nor have R. C. Romba and I, in unpublished research on height and weight in several primitive and cosmopolitan populations. Range restriction cannot explain our failure to find the expected increase, nor should fixation by random gene loss work in this way for polygenic traits.

One possible mechanism for the seeming constancy of metric variation is stabilizing selection. As already mentioned, I have found evidence for stabilizing selection in two relatively unacculturated Solomon Island tribes, where men of midrange height had more children than shorter or taller men. Assortative mating would increase variability in the same way that

inbreeding does, but it has not been found for stature outside of Western European and American populations. Some Solomon Island groups do mate assortatively for skin color, however.[43]

To close this brief account, one might note that no population in the real world whether "primitive" or technologically advanced, satisfies the requirements for the Hardy-Weinberg equilibrium, the cornerstone of population genetics. Human mating is never random; inbreeding, assortative mating, and selective mating are the rule, rather than the exception. It is a tribute to the robustness of its formulation that the Hardy-Weinberg rule works as well as it does.

SUMMARY

Human evolution did not occur once and for all, far away and long ago; it is continuing among ourselves, here and now. The goals and the means are the same, but some of the rules of the game have been changed. The goal is still adaptation to an environment, now man-made rather than natural; the means are still selection - again, human rather than natural - working on a store of heritable variation. The human germ-plasm which provides heritable variation has been little affected by man so far, except for permitting survival of previously unfit genotypes and for introducing mutagens, both on a scale insignificant in population terms. Whereas natural selection works mainly by death control, human selection in advanced societies works by birth control (since death rates have been dramatically lowered). Most persons in advanced societies now survive to reproduce a small number of offspring, reducing the scope within which selection can work.

Prominent trends in ongoing human evolution are the breakdown of breeding isolates, with heterosis a remote possibility; environmental homogenization, removing a former cause of racial diversity; environmental amelioration, permitting full genotypic expression of traits, like body size and rate of maturation; substitution of the diseases of civilization for the infections and malnutrition of primitive man; emphasis on mental rather than physical traits as a selective force; and the increasing numbers of mankind, at once a cause, an effect and a limiting factor in man's further evolution.

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SECTION II

EVIDENCE OF GENETIC CHANGE IN HUMAN POPULATIONS

Morton S. Adams*

INTRODUCTION

Genetic change in a population can be manifest as a change in the kinds of genes or in the frequency of particular genes. The major thrust of genetic counselling and medicine in general is concerned with the kinds of genes in a population with particular emphasis on genes with deleterious effects. Many of the papers in this Symposium are concerned with this important aspect of "Heredity and Society". This paper will discuss changes in the frequency of genes in the population in a descriptive way and illustrate how changes in cultural phenomena may influence the genetic makeup of a population. I will focus first on a study of isolation and local genetic differentiation followed by an anecdotal account of the breakdown of isolation. Finally, I will consider trends in genetic admixture of the American Negro.

I. ISOLATION AND LOCAL GENETIC DIFFERENTIATION

Southwestern Indian tribes provide much insight into these processes. Field work with the Papago tribe who live in the Sonoran desert along the

*Supported in part by Contract #C-20455, New York State Birth Defects Institute.

Mexican border in Southern Arizona has been reported in a series of papers (Adams, et al., 1970; Niswander, et al., 1970 and Workman and Niswander, 1970). Approximately 5000 Papago reside on the 2,774,000 acres of the reservation. The desert is hot and arid. Rugged mountains to 8000 feet are separated by broad valleys. There is no permanent water except in springs in the mountains.

The prehistory of this tribe goes back to 8000 B.C. Archeological evidence of continual habitation is firmly established. Whether these ancient peoples were genetically antecedent to the present day inhabitants is unknown. However, in 100 B.C. the Hohokam brought agriculture from the south. In 1300 A.D., the Salados (builders of the multi-storied houses such as those still extant in Casa Grande, Arizona) came into the desert from the east as the Pueblo people were forced west by the invasion of the Athapascans from the north. The fate of the residents of the great houses was sealed before the Spanish arrived in the 17th century as they found the great houses abandoned and the people spread out over the area. Our best guess is that the gene pool of the Papago received contributions from both the Hohokam and the Salados.

In 1680, a Jesuit, Father Kino, first contacted these people and traveled extensively among them. He estimated the population to number 10,000 and observed it to be divided into five groups:

1. Sobipuris (East along the Santa Cruz River),
2. Gilenos (along the Gila River),
3. Pima Proper (Northern Sonora),
4. Soba (Northwest Sonora)
5. Papago (Southwest of the Gila and Santa Cruz Rivers).

From about 1690 until 1860, the Apache formed the eastern boundary of Papago lands. This was a

very important influence since for 150 years the Apache pillaged and terrorized the Papago villages. Prior to the coming of the Apache, the Papago lived in small isolated villages widely dispersed across the desert. They had summer residences near their crops and winter homes near permanent wells and springs in the mountains. With Apache pressure they were forced to retreat to a small number of large defense villages. These persisted until the Apache were subdued, at which time, the Papago dispersed again into new villages. The dispersion was along family lines and the new villages maintained cultural ties with the defense village. The reservation today is subdivided by other factors. Next to family and village, dialect is the most important social entity. Dialect groups are related to the groups recognized by Father Kino. Finally, in 1935, the reservation was divided into ten political districts for tribal council representation along dialect and defense village lines. These units have not changed in the over 300 years since Father Kino visited, probably because they are based on dialect, marriage pattern, festivals and ceremonies, competition in sports, cattle round-ups, cactus groves, well site utilization and topography.

A sample of 709 individuals from 433 nuclear families were typed for 24 genetic polymorphisms including blood groups and serum proteins. We found highly significant differences in gene frequencies among the districts. For each locus the genotype frequency of each district was compared jointly with the frequency in the total population with a chi square contingency table analysis. The hypothesis tested maintained that the differences in genotype proportions among the 10 districts are no greater than among 10 random samples drawn from the total population. Most of

the comparisons were significant at the 5% level. This suggests significant difference in the pattern of genetic variation among districts. These differences may reflect differences in ancestral gene frequencies. There is evidence that the different districts were derived from different ancestral groups. Dialect difference may also reflect this diverse ancestry. We can't tell the magnitude of these effects but since there are no large genetic differences among the Indian tribes of the southwest, cultural differences without genetic variation may have existed. It is also possible to compare genetic distance with geographic distance for pairs of districts. Figure 1 illustrates this analysis. In this figure, genetic and geographic distance from District 4 to Districts 1, 2, 5-8 is shown. The correlation coefficient is $r = .894$. This analysis reveals that almost 50% of the genetic variation among districts can be attributed to the effect of isolation by distance. Finally, genetic drift would likely increase the genetic differentiation since these districts contain from 300 to 1000 individuals and have been highly endogamous for 250 to 300 years.

II. BREAKDOWN OF ISOLATION

As effective as isolation is in the establishment of significant genetic differences between populations, a cultural change can effect this pattern in a few short generations. No data is available on the Papago to illustrate this point. However, several teams of medical students have worked in towns surrounding the Hopi Reservation in Arizona. (Kunitz, et al., 1971) These students have interviewed all Hopi Indians who have left the reservation to take up residence in the towns of Flagstaff and Winslow, Arizona.

Among the most striking data gathered concerned the percentage Hopi-non-Hopi marriages among those who have left the reservation (Table 1). Among reservation Hopi, a non-Hopi marriage is a distinct rarity. However, we see that by the 2nd generation off reservation between 67-83% of marriages are out marriages.

III. TRENDS IN GENETIC ADMIXTURE IN THE AMERICAN NEGRO POPULATION

The analysis of intermixture in a dihybrid population entails estimation of the proportion of the hybrid gene pool derived from each parental population. We do not have information on gene frequencies in Negro populations in Africa during the eighteenth and early nineteenth centuries; in place of these unknown frequencies, averages of gene frequencies found in appropriate tribes in the present time are used. In theory, a large number of genes could be used, however, for many the gene frequencies of the two races are too nearly alike. The frequency of other genes are subject to modification by the differential survival of various zygotic types; these survival patterns are not the same in the United States as they are in Africa. Such genes cannot be used.

To make our study comparable with the earlier studies (Glass and Li, 1953), we chose the following four alleles and studied a sample of Negro patients admitted to Strong Memorial Hospital in Rochester, New York (Table 2). Our estimates of admixture are typical of other studies of urban Northern populations. For purposes of discussion, the distribution of skin color of this sample is shown (Figure 2). Skin color was coded by an experienced genetic field worker and is taken only as an approximation of percentage

admixture for purposes of illustration. The mean of this distribution is between color codes 3-4. If we superimpose a scale of percentage admixture with a similar mean, some interesting projections can be made. This curve is truncated. At approximately 25% African genes, persons are no longer identiable as Blacks and these genes have left the gene pool of the American Negro. Of course, these are the same genes most of which historically entered this gene pool during the eighteenth century. Thus, there is a tendency towards a new equilibrium dependent upon continuing admixture and the intensity of assortative mating for the percentage admixture. Both these factors are strongly culturally bound and as cultural changes they will reflect the trends.

One factor in particular which is important in this regard concerns residential segregation. The trend over the last decade has been to increasing segregation despite legislative changes and judicial decisions. Rochester, New York is typical of most urban areas. Between 1960 and 1970 there was a net loss of 16.6 percent of the white population out of the city, while blacks had a net gain of 52.0 percent (Farley and Taeuber, 1968). Certain evidence indicates that the rate of in-migration of blacks has decreased, however, due to the age structure of the population, the city will have a continued increase in the proportion of black residents. The Negro population in Rochester is youthful, with many women in childbearing ages and many more about to enter these ages. The white population is not only out-migrating but also more elderly. In fact, only 17% of whites, compared with 44% of blacks, are under age 15. Residential segregation is increasing, too. Comparing the minimum percent of Negroes whose census tract would have to be changed to obtain

a homogeneous distribution of the two groups, in 1960 this was 76.7 percent and by 1965 it had risen to almost 80%. This combined with assortment of mates by percentage African genes will effectively increase the genetic distance between the two populations, a factor of some importance to public health and education planners.

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Table 1

Estimation of the Proportion of Migration That Has Occurred From White to Negro Population in Rochester, N.Y. p_1 = Estimated Gene Frequency in Ancestral Negro Population, p_2 = Observed Gene Frequency in American Negro Population of Rochester, N.Y., m = Estimated Percentage Admixture.

Allele	p_1	p_f	p_2	m
R^o	.62	.49	.03	.213
R^1	.06	.14	.42	.225
I^A	.17	.14	.08	.333
I^B	.15	.18	.25	.300

$$m = \frac{p_f - p_1}{p_2 - p_1}$$

Table 2

Pattern of Marriage Among Hopi Indians Residing Off Reservation in Winslow and Flagstaff, Arizona

WINSLOW, ARIZONA			
1st Generation off Reservation			
Hopi - Hopi	.70		
Hopi - Other Indian	.26		
Hopi - Non-Indian	.04	>	.30
2nd Generation Off Reservation			
Hopi - Hopi			
Hopi - Other Indian	.42		
Hopi - Non-Indian	.25	>	.67
FLAGSTAFF, ARIZONA			
1st Generation Off Reservation			
Hopi - Hopi	.70		
Hopi - Other Indian	.22		
Hopi - Non-Indian	.08	>	.30
2nd Generation Off Reservation			
Hopi - Hopi	.17		
Hopi - Other Indian	.54		
Hopi - Non-Indian	.29	>	.83

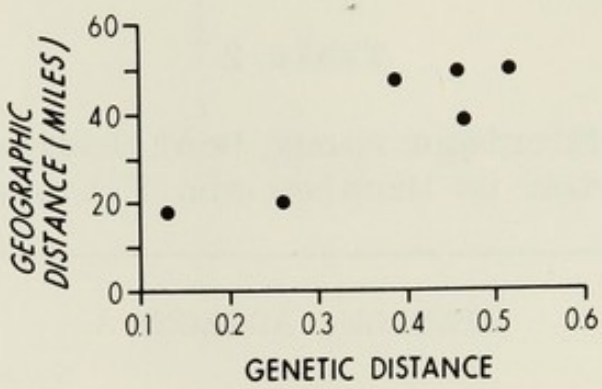

Figure 1. Geographic and genetic distance between District 4 and Districts 1, 2, 5-8.

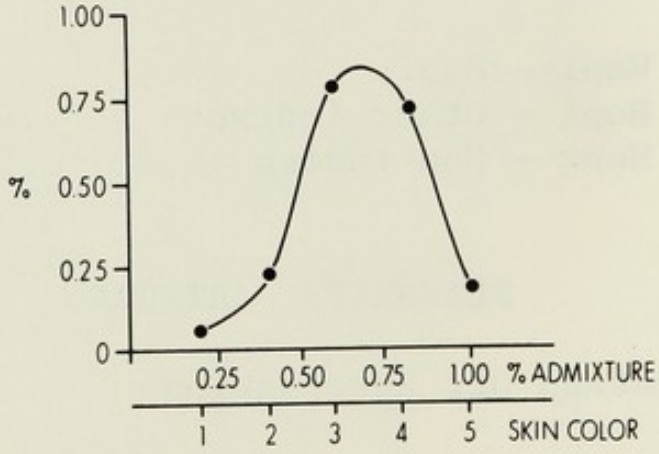

Figure 2. Distribution of skin color in a sample of American Negroes.

DISCUSSION

VIRGINIA APGAR (National Foundation-March of Dimes, White Plains, New York): Would you tell us how you code skin color?

DR. ADAMS: An experienced social worker graded the skin color completely arbitrarily. Different methods have been used for grading skin color and skin reflectance is one of the favorites. Our study was crudely done and was not done with this use in mind. That is the reason I was so hopeful we would have our data on genetic admixture from our other method which doesn't rely on anything as arbitrary as color coding. Incidentally, other studies of skin color using this method were done in Brazil and have revealed the same results as those having used more accurate methods. But I don't think any of them are entirely satisfactory.

DR. PORTER: In addition to yourself, in Rochester, and Dr. Bently Glass, in Baltimore, who has done studies of this type?

DR. ADAMS: Peter Workman has recently summarized this work in Social Biology. They have been done in southern cities and in Chicago, Baltimore, New York and Hawaii. There have been a lot of studies of racial intermixture in Hawaii specifically relating to the residential segregation material I'm talking about.

DR. PORTER: It is interesting that your figures are much the same as Dr. Glass's. Do you know the figures from Chicago and other parts of the country?

DR. ADAMS: They average out to be around 25 to 30% of the average black American. One of the important things to recognize here, and one of the things I had hoped to bring out for you, is that it does not say anything about individuals. The distribution of percentage admixture I do not think is known. That is the point I was trying to make with the skin color.

DR. MOTULSKY: Is it not true that when admixture studies were done in the deep South, the percentage of mixture was lower than usual?

DR. ADAMS: The rural deep South. Yes.

DR. MOTULSKY: Could you comment on the reasons - the history and dynamics?

DR. ADAMS: It is thought that the greatest influx of western European genes into the black American population took place in the early generations of slavery. Perhaps the first two. If you make this kind of postulate, and historically it seems to be a valid one, you can show that the type of distribution that I was postulating with skin color would prevail, given a small amount of continued in-migration and a small amount of assortive mating which will stratify for skin color: namely, if you are getting light marrying light, then this will then be truncated as passing for white. Why urban blacks are different from rural blacks may be because the rural blacks, who migrated to the urban North, were not a random sample of the population in the rural South but were distributed more along the admixed rather than the pure African. This is purely hypothetical.

DR. GORDON: When you are discussing the

proportions of ancestral genes in the present Negro population, you cited the ABO blood groups; a couple of ABO genes and a couple of rhesus genes. But when one looks at a long tabulation of other genetic markers - enzymes, serum haptoglobin types and others - the consistency is not quite as good. Is it because one finds that there are different proportions? We did studies using about thirty markers on the hybrid colored population of Capetown and although we got quite consistent results, more or less, as we analyzed different genetic markers there were one or two curious standouts which are a little odd. The rhesus negative gene was the most striking because we found far less of this in the colored population than the findings in other genetic markers might have predicted. Is this a selectant or is this an accident of analysis?

DR. ADAMS: Well, there are several possibilities. Analysis of the systems Dr. Gordon mentioned have yielded anomalous results. By anomalous, I mean that given the amount of gene flow found, based on the results in the majority of your genetic systems, several of the others have shown a disproportionate increase or decrease in gene flow. Sickle cell, as has been mentioned earlier, is the classic example. It looks as if you have much more admixture if you compare sickle cell trait incidence between the African and European population. But the reason here is obvious. The selective milieu has changed and the sickle cell trait is being selectively eliminated here, whereas in Africa it is being selectively maintained. For other genes, such as haptoglobin, there is not yet definitive evidence of this type of selection at present. I think that if we look in diverse populations, such as those in Capetown and in

Brazil and in this country, we do see these anomalies. It is very tempting to say that this is evidence for selection. However, until I feel more confident that I can postulate some selective mechanism such as for sickle cell trait, I would hate to attribute too much to selection as accounting for these differences.

ANDREW Z. KELLER (Veterans' Administration, Washington, D.C.): I found it very difficult to follow your lines of reasoning based on skin color because I personally go through about three or four changes of skin coloring each year. Usually our children might be rather light complexioned and as they get older they tend to get darker. Did you make an adjustment for age?

DR. ADAMS: No, and I don't want to stand on this skin color point strongly. I am using it as a basis of discussion. What we are aiming for is a method of determining an individual's percentage admixture by the use of all these various genetic markers that Dr. Gordon has mentioned. You see, then we have something that is not a factor when mates are chosen. These factors, then, are not going to change depending upon whether one lives and works outside in Alabama or in Boston. So, this is the reason that we want something other than skin color.

JOHN GIBBON (Suffolk State School, Melville, New York): There was one rather interesting correlation that I thought appeared in your studies of the Indian intermarriage and that was the majority, actually, of the intermarriages that occurred were with other Indian tribes. You have, roughly, let's say about 25% (more or less) outside and 50% with other Indian tribes. There is, perhaps, an interesting correlation with the

degree of hybrid which I suspect is not a single variable but an incident variable. That is, your hybrid occurs where you have a closely related but slightly different strain and drops off as the strain genetically becomes more and more different, so that you begin to lose in your gross cross-matches where you have considerably different genetic composition. You begin to lose the effect of hybrid vigor again and, as we all know, you reach a point where crossbreeding does not occur at all. Rather it is non-fertility, so that I suspect your hybrid vigor is a variable and not a simple factor just as the other human characteristics are a continuous variable. It is interesting that the selection of mates by the Indian tribes follow this kind of reasoning. In fact, we are often attracted to mates who are somewhat similar yet enough different - but not grossly different. And this is the general trend in population. I think the psychoanalytic implications are quite apparent, too, besides the more solidly genetic factors.

DR. ADAMS: I have identified at least two areas that I would like to comment on. One is that the choice of mates is very strongly related to where you live. The non-Anglos in Winslow and at Flagstaff very definitely are segregated residentially. Into this mix, also, goes Spanish-speaking Mexicans - many of the Indians also speak Spanish - so it's dependent upon who you mate with and, in large measure at least, who you are associating with culturally especially in these cities in Arizona. The second area - and this is a large area which I really don't think we can get into - is one in which the key point is that where heterosis has been found in plants and less so in animals, it has been among inbred strains, not necessarily

closely related ones. It seems to be something to do with the inbreeding and then the subsequent cross-breeding that leads to the heterotic effects.

HUMAN BEHAVIOR, GENES AND SOCIETY

Arno G. Motulsky
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Biologic basis and evolution of human behavior.

Our understanding of the biologic basis of life rests upon a firm theoretical framework, comprising the inherited information passed from generation to generation in the DNA code of the germ cells and embryological processes of differentiation of all the different tissues from the fertilized egg. One of the hallmarks of human biology is the individuality of man. Based on current tests for blood groups, blood enzymes, plasma proteins and histocompatibility antigens, every person on earth appears to be different except for identical twins.[1,2] Our species, therefore, is extremely heterogeneous. While no direct evidence is available, it is likely that the genetic substrate of behavior (including central nervous system and endocrinologic functions) shows similar individuality.

The chromosomes and genes of each body cell are identical, but differentiation leads to the expression of only a fraction of genes in specialized cells.[3] Only 5 - 10 percent of all genes are active in a given cell, including those genes required for basic metabolism and protein

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Supported in part by NIH grant GM 15253.
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synthesis in all tissues. Brain cells utilize some genes not active in kidney, liver or heart, and vice versa. However, recent evidence suggests that a higher proportion of genes is active in brain than in other tissues.[4] In dealing with the evolution of human behavior, one is impressed that man has built upon pre-existing sense organs, integrated motor systems and complex reaction patterns, the higher human functions of abstract, conceptualized thought and language. The evolutionist Rensch[5] has traced the development of nervous systems from the irritability of the amoeba to the characteristics of man and has concluded that evolution has brought increased complexity without altering basic processes of cell-cell interaction and excitability. Detailed studies of primates suggest that many aspects of human behavior, including even symbolic language, may be achieved by chimpanzees.[6]

Primates and other animals have been studied for sexually dimorphic behavior and for the effects on female offspring of testosterone administration to mothers during gestation.[7] "Male dominance" is not unique to modern western societies but has been observed in practically all developed and primitive human societies as well as in other mammals. In these days of women's liberation we may note that biologically based differences in behavior patterns most likely exist between the sexes. Nevertheless, the fact that a significantly higher proportion of women have passive "feminine" stereotypes of behavior and, conversely, that a higher proportion of men exhibit aggressive "masculine" stereotypes of behavior probably has a major biologic basis interacting with social conditioning.

Some aspects of the biological substrates of human behavior are remarkable.[2] About one and

one-half million years or 85,000 generations ago, at approximately the beginning of human history, the capacity of the human brain was only 500 cc. as estimated from skull sizes. The capacity of the brain increased to the present size of approximately 1300 cc. before man used this brain capacity for peculiarly "human" activities. Evidence of cave painting and the beginning of languages appeared only 50,000-60,000 years or 2500 generations ago. This biologically short time span provides little room for further evolution, yet human culture evolved dramatically. Agriculture started 10,000 years or 500 generations ago, urbanization 6000 years or 300 generations ago, and scientific industrialization only in the last few hundred years - just a fleck of time on the evolutionary scale.

Table 1 summarizes some of the similarities and differences between biological and cultural evolution,[8] the most important difference being in the time scale of events. Within cultural evolution, we might recognize the special role of technological inventions, such as radio and television, whose impact rapidly has been felt in our life time, while social structure and family patterns change more slowly. Another important contrast is the directedness of change in the cultural sphere, in which new ideas are purposeful. Biological evolution depends upon random mutations in the DNA, only rare mutations being suited for a selective advantage in the survival of the species. In the broader sense, cultural changes also may be harmful or unpredictable in their impact on people or the environment or even the long-term survival of man. The use of symbolic language appears to be the central distinguishing feature of human culture. Whether language development required a saltatory change in the biological structure of the brain of early

man or whether language itself developed only gradually from styles of communication and integrated nervous system functions in other animals is not known. However, a mechanism for saltatory developments at the genetic level does exist: chromosomal duplications can lead to the formation of genes with entirely new functions.[9]

Genetic basis of normal human behavior.

Complex behaviors do have genetic bases, presumably expressed in the function of the brain. Selective breeding of dogs, mice and other animals for aggression, emotionality, activity levels, strength of sex drive and maze-solving have a genetic basis.[10,11] A search for comparable evidence in man requires special methods of analysis. Family studies and even twin studies are confounded by the fact that both heredity and environment are shared in the family unit. The relative effects of genotype and environment on human behavior can be best distinguished by study of monozygotic, identical twins who were reared apart from birth or shortly thereafter. Data for personality characteristics - extraversion, neuroticism, mannerisms[12] - and I.Q.[13] indicate considerable correlation between genetically identical co-twins who were raised in different homes.* Another potent method for distinguishing genetic and environmental effects is the investi-

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*Some of the most interesting data exist in the form of anecdotes. For example, two identical twins in England who had never seen each other, but were found by the follow-up investigation, were married, in their forties, both door-to-door salesladies, playing minor parts in amateur theatricals, keeping lots of animals at home (12, pp. 200-202).

gation of behavioral traits and disorders among both the biological and the adoptive relatives of individuals who were adopted early in life (see below - schizophrenia). Even when genetic factors can be clearly inferred by such investigations and corroborated by other lines of evidence, the patterns of transmission, let alone the action of the particular genes involved, are unknown.

Certain sensory processes can be affected by specific mutations such as red/green color blindness or tasting of phenylthiocarbamate. As a result, affected individuals perceive colors or tastes quite differently. Investigation of individual differences at the level of the sensory input apparatus has been neglected in man, though striking progress on behavioral mutants primarily at the level of sensory processes has been reported[14] for the fruitfly!

Extensive studies of the normal human electroencephalogram (EEG) have been carried out by Vogel and his colleagues.[15] Twin and family studies indicate that the pattern of EEG activity is highly individual and almost completely determined by polygenic inheritance. Nevertheless, several common variants of the pattern affecting amplitude or frequency were found. Family studies showed that these variants were determined by the effect of a single dominant gene, superimposed on the overall polygenic background. Limited data on spouses even suggest that for one or two types of EEG patterns there may be assortative mating - that an individual having a certain type of EEG pattern is more likely to marry a person having the same EEG pattern. Perhaps certain personality attributes are associated with particular EEG patterns.

Another line of evidence that personality traits may be "inborn" comes from observation and

testing of newborn infants. Freedman and Freedman[16] used a Brazelton rating scale for 25 behavioral characteristics to compare Chinese-American babies with a control group of Caucasian babies in San Francisco. They found that sensory and motor development, CNS integration and interest in the environment were the same for the two groups, but that the Chinese babies were less perturbable, less changeable and consoled more easily. If confirmed, such findings suggest that stereotypes of oriental inscrutability and stoicism may have some foundation in early behavioral responses and possibly may be genetically determined. It would be interesting to compare babies of Chinese mothers and fathers in Chinese-American matings, to evaluate the role of intrauterine environment. Similarly, sensorimotor development is significantly precocious among American Negro babies.[17] Such differences measured in infancy appear to have no correlation with later intellectual performance and personality traits.

Genetics of abnormal human behavior.

Among human behavior disorders, schizophrenia has been extensively studied and has major genetic determinants.[18] The more closely related a person is to a schizophrenic patient, the higher the chance of schizophrenia in the relative. Monozygotic twins have a high concordance for schizophrenia, much higher than dizygotic twins. But the strongest evidence for genetic rather than just intra-familial environmental determinants in schizophrenia comes from adoption studies. Heston,[19] for example, compared the life history (up to a mean age of 36 years) of individuals separated as infants from schizophrenic mothers with a control group of such adopted individuals whose mothers were not

schizophrenic. The frequency of schizophrenia in the separated children who had schizophrenic mothers but grew up in non-schizophrenic homes was about 10% (5/47), versus none in the control group of 50. In addition, the children of schizophrenic mothers had a significantly higher incidence of difficulties with the law, low I.Q. and behavioral troubles in the military. Complementary studies were carried out in Denmark, starting from schizophrenic individuals who were adopted early in life and looking at the frequency of schizophrenia and related psychopathology in the biologic and adoptive relatives of the probands.[20] Again, the excess of schizophrenic illnesses fell on the biologic relatives and not among the adoptive families. Although a single dominant gene could account for a predisposition to schizophrenia in at least some cases, it appears likely that multiple genes are involved. The situation is similar for affective illness, especially manic-depressive psychosis,[21] and probably for certain behavioral disorders of childhood.[22] It is extremely important for counsellors, psychiatrists and psychologists to be aware of such genetic predispositions. Parents often are distraught and guilty over their possible responsibility for the behavioral problems of their children whereas the "fault" may lie in the biologically determined aspects of personality development. Occasionally, specific biochemical and chromosomal abnormalities may be recognized. For example, XYY and XXY (Klinefelter's syndrome) males have an abnormal complement of the sex chromosomes and have an enhanced risk of psychopathology and criminal behavior. It has been reported that XYY males differ from their XY cohorts in maximum security prisons in Scotland in that the XYY males come from apparently "good" homes, have no siblings with prison

records, direct their crimes against property rather than people and have less capacity to recognize their wrongdoing.[23] The analogy could be drawn to the pathologic forms of mental retardation, in which a child of normally intelligent parents has a genetic or developmental cause of dysfunction of the nervous system. In fact, however, recent efforts to confirm the psychological characterization given above for XYY males have failed to show such differences from XY fellow prisoners (see 24). In addition, population screening among newborns reveals XYY to be remarkably common, constituting about 1 per 700 male births. Obviously, most XYY males are among the "normal" men of our society rather than locked up in prison. The risk for crime, however, presumably is higher than for the XY males.

XXY males have been studied more carefully. These men are infertile because of hyalinization of the testes, and they often have mild mental retardation, social immaturity and criminal tendencies. It was suggested that their behavioral problems might be a reaction to their own and others' response to their effeminate body habitus, occasional gynecomastia and hypogonadism. However, Nielsen and his colleagues in Denmark compared 34 XXY and 16 XY men, all severely hypogonadal and attending a male infertility clinic. The XXY men were less mature, less secure, less proficient verbally and lower in self-esteem than their XY hypogonadal counterparts, suggesting that something about the chromosomal constitution rather than just the body image, led to the behavioral abnormalities.[25] Another sort of psychologic defect has been demonstrated in patients with Turner's syndrome or gonadal dysgenesis, associated with a 45,XO karyotype. These girls score better on

verbal than non-verbal I.Q. tests, the difference being due to tests of space-form perception.[26] On Draw-A-Person or Design-Copying tests they often have great difficulty. Just how such a chromosome abnormality affects a seemingly specific cognitive function is altogether unknown. However, an analogy has been drawn to the Gerstmann syndrome, which results from strokes or tumors damaging the dominant parietal region causing defects in space perception, right-left discrimination, writing and calculating.

Biologic traits and alcohol effects.

Simple biologic traits may be clues to individual differences in the physiologic effects of alcohol When German males were categorized into three groups according to the amount of chest and body hair, those with relatively little body hair had a significantly increased risk of developing cirrhosis of the liver due to alcoholism.[27] It is conceivable that male hair distribution, testosterone secretion, alcohol metabolism, and liver function may be interrelated.[28] Certainly alcoholism is one of the major medical and social problems in this country and cirrhosis of the liver an important cause of death. Alcoholism apparently has strong biologic determinants. The frequency of alcoholism among the genetic relatives of index cases adopted early in life is six times higher than among their adoptive relatives, in half-sib studies recently reported.[29] There is also evidence to support the lay contention that individuals differ remarkably in their tolerance for alcohol and in the effects of drinking. In Alberta, Canada, police officers observed that it took longer for Eskimos and Indians of that region to "sober up" than for

Caucasians. Studies of the metabolism of ethanol in these groups demonstrate that intoxication is achieved at similar blood alcohol levels, but that the elimination of ethanol from the blood is slower in Eskimos and Indians than in the Caucasian group.[30] Another ethnic difference is the propensity of Orientals to flush upon drinking alcohol. Wolff[31] showed that Oriental infants already demonstrate such ethnic difference in flushing and in blood flow monitored through an ear lobe in response to ethanol.

Interaction of heredity and environment.

Hereditary predisposition to such exogenous agents as alcohol and other drugs constitute an example of gene-environment interaction in human behavior. Even better models have been developed with inbred mouse strains. For example, DBA mice are highly susceptible and C57BL mice highly resistant to seizures after an auditory stimulus.[32] Yet even in the DBA mice the stimulus must be given at a sensitive period in development in order to demonstrate the effect. Also a hybrid between the two strains has intermediate susceptibility, so that the frequency of seizures in the hybrid strain varies with "how hard you blow your whistle"! Other examples of interaction of heredity and environment are found in the cultural evolution of man, including the spread of the gene for sickle hemoglobin with the slash and burn agricultural technique that led to stagnant pools for the proliferation of mosquitos and malarial parasites.[33] As malaria became endemic, the selective advantage of the sickle cell trait condition vis-a-vis malaria led to an increased frequency of the sickle gene.[34] Lactose intolerance is another interesting example. All over the world, especially among Black and Oriental populations, large numbers of people who

are unable to digest lactose in milk develop symptoms of diarrhea and gas from lactose intolerance.[35] Caucasian populations, long accustomed to domesticated milk-producing animals and milk-drinking through adult life, typically have the reverse situation with 90% of the population lactose tolerant and only 10% intolerant. Possibly all humans were lactose intolerant at one time, but the development of agriculture with cattle yielding milk for human consumption gave an advantage to those individuals with mutations allowing digestion of lactose after weaning and in childhood. A 1% advantage in fitness (survival and fertility) in about 400 generations could account for the marked difference in gene frequency for lactose intolerance in different populations.[36]

It is customary to speak of selective advantage with regard to gene frequencies. However, selection acts on the whole individual, as affected by the particular gene allele, and in the context of society. Thus, it is appropriate, as Wright has suggested,[37] to attempt "cost/benefit" analyses of the costs of given genotypes compared with their contributions to society. Societal costs and contributions are difficult to assess quantitatively and the relevant medical, psychiatric, genetic and sociologic data often do not exist. Further development in this aspect of societal genetics will be of great general interest.

Heredity and I.Q.

Genetic studies of intelligence, as measured by I.Q. tests, have generated much unfortunate controversy in recent years. It has always been known that some individuals were "brighter" and learned faster than others. Common sense observations also recognize very "bright" children

from families of poor learners and some not-so-bright children from very bright parents. Thus the parental and school environment alone could not account for all these differences. Galton,[38] a century ago, qualitatively rated people's intelligence and obtained a bell-shaped distribution with an excess of individuals at the very low end. Binet in Paris, 60 years ago, began developing quantitative tests of "intelligence" that could be shown to correlate with school performance. Using arbitrary test items, children answered correctly an increasing proportion of items as they became older; for any given age, a certain number of items was determined to be the average performance. An I.Q. or intelligence quotient represents, then, the age-average performance of the child divided by his chronological age, normalized to a median score of 100 and a standard deviation usually of about 15. Obviously, the test items devised by psychologists bear no known relationship to biologic units of nervous system cognitive function; certain important biologic functions may not be covered at all by the usual test items. Relevance of "I.Q." tests for correlation with school and job performance has been established only for western industrialized culture. Herrnstein[39] has recently summarized certain data that relate I.Q. not only to school performance, but beyond that to occupation and social position. Again, it must be emphasized that one is dealing with distributions of scores, so that bakers, for example, include some individuals with high I.Q.'s but their average I.Q. score is lower than that of accountants, engineers or physicians. To succeed in these professions a person requires a higher minimum I.Q. than in many other occupations less dependent upon abstract problem-solving. Correlations

of I.Q. according to degree of relationship indicate that monozygotic twins are closely concordant in I.Q. (whether raised together or raised apart), while fraternal twins or sibs or parent-child pairs have the expected 0.5 correlation. Unrelated persons living apart have zero correlations, while unrelated persons reared together have a correlation of 0.2, indicating the relative role of environmental factors.[40] A similar estimate is derived from the discordance of monozygote twins reared apart (0.18).[13] Just which genes are involved is unknown but the statistical interpretations suggest polygenic inheritance. Such a complex trait as intelligence seems likely to be based on the interaction of many genes. On the other hand, polygenic inheritance can be simulated by relatively few genes. The fewer the genes involved, of course, the better the chance of finding out what they are and how they act.

Mild mental retardation illustrates the effect of polygenic inheritance. Siblings and parents of such mildly retarded individuals tend to have lower than average I.Q. consistent with the expectations of polygenic inheritance.[41] On the other hand, siblings and parents of children with very severe mental retardation tend to have normally distributed I.Q. scores, because the severe disturbance of mental development reflects the superimposed insult of some particular recessive genes, chromosome aberration, trauma or intrauterine infection. Also, there is a phenomenon known as regression toward the mean, so that children of lower than average I.Q. parents tend to have I.Q.'s higher than the parents.

The search for neurological correlates of intelligence has led recently to the use of cortical evoked potentials. It has been claimed that

individuals of superior I.Q.'s have shorter latency in evoked potentials,[42] possibly reflecting information processing in the nervous system. Such findings require confirmation, genetic study and cautious interpretations.

In a meritocratic society, as aimed at by western industrialized capitalist and socialist societies, each person is to achieve an educational, occupational and social level consistent with his ability and motivation. Those individuals with the genetic potential for high I.Q. tend to professional and managerial status while those with lower I.Q. end up in the lower economic and social classes. Marriage partners already tend to resemble each other in I.Q. With such assortative mating of a genetically determined trait such as I.Q. and with free social mobility so that high I.Q. persons move up and low I.Q. persons move down the social ladder regardless of family connections, we will tend toward a society stratified by genetic intellectual potential.[39] There is the possibility, of course, that a larger proportion of bright young people will reject the social forces that motivated their parents to seek the "rat race" for educational and social status, leaving a pool of high I.Q. genes in the lower social classes. Nevertheless, an open meritocracy with free social mobility may have far-reaching ultimate genetic consequences.

The genotype with regard to intelligence is expressed in an environment that includes most importantly the family and the schools. The relative contribution of genetic factors depends to some extent on the variety of environmental experiences. We have no idea whether the full genetic potential of individuals is being achieved under present circumstances; enriched environments may do much to improve the measured

I.Q.'s of individuals though such enrichment may have to be highly individualized.

I.Q. differences in populations.

Finally, we and others have agonized over the possible meaning of the differences in tested I.Q. score distributions for white and black persons in the United States. Using a normative white sample, with a mean I.Q. of 100, samples of black children give distributions around a mean I.Q. about 15 points lower.[43,44] There are differences according to whether the whites or the blacks were from the southern states (both groups score lower), but many studies indicate an approximate difference of 15 points or one full standard deviation. Whatever the cause of the differences, such a situation presents a tremendous problem for the educational system. Blacks will have a much higher proportion of children falling below a certain I.Q. point and be recognized as slow learners in the schools. There is great overlap, with occasional blacks scoring as high as the highest scoring whites, but the proportion of blacks scoring in the lower range of I.Q. is significantly higher and those in the upper range significantly lower as compared with the white population. If, for example, an I.Q. of 115 or above were to be used as a criterion for admission to universities or to professional schools, only 2 percent of blacks would qualify compared to 16 percent of whites. What are the causes of such measured I.Q. differences between blacks and whites? First, there is long-standing discrimination against blacks in educational opportunities. Second, there are major differences in socio-economic status. It is known among whites that I.Q. and socio-economic status are significantly correlated, probably for both environmental and genetic

factors. If socio-economic status is "equalized", the I.Q. scores of blacks remain lower than those for whites. Again, it can be objected that the environments of the upper socio-economic classes in whites and blacks are not identical. Third, ethnic, presumably inherited, factors may be important. Recent data in I.Q. scores of other socially disadvantaged groups like Mexican-Americans or American Indians provide comparisons with the performance of black children.[45,46] With Mexican-American children of lower social class than the black children, the black children did better on culture-dependent tests but worse on culture-independent, abstract material. Since the various studies which clearly indicate the significant role of heredity on I.Q. determination were only done among white populations and since obvious environmental differences exist between the races, the relative roles of genetic and environmental factors in the observed differences in I.Q. tests of blacks and whites simply have not been established. One must admit, however, that there are biologic differences in gene frequencies of many traits between different populations and that differences may exist for the genes involved in intelligence. The direction of this difference *a priori* is unpredictable on biologic grounds. It remains possible, therefore, that at least some of the observed differences in I.Q. between populations may have a genetic basis. However, in a country which claims to value individual liberty, the emphasis should be upon the individual, upon the provision of a variety of school and pre-school environments that may stimulate more of our youngsters to achieve their full potential. While we seek understanding of the biologic basis of cognitive functions in man and feel that existing data on population differ-

ences must be considered for education policies, we do not support suggestions that a major national effort be directed to studies of racial differences with so artificial a parameter as I.Q. scores. The methodologies currently available cannot give unambiguous interpretations and, most importantly, the current political climate may generate deliberate misinterpretations of any findings.

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Table 1

COMPARISON OF BIOLOGIC AND CULTURAL EVOLUTIONS

	Biologic evolution	Cultural evolution
Mediated by	Genes	Ideas
Rate of change	Slow	Rapid and exponential
Agents of change	Random variation (mutations) and selection	Usually purposeful. Directional variation and selection
Nature of new variant	Often harmful	Often beneficial
Transmission	Parents to offspring	Wide dissemination by many means
Nature of transmission	Simple	May be highly complex
Distribution in nature	All forms of life	Unique to man
Interaction	Man's biology requires cultural evolution	Human culture required biologic evolution to achieve the human brain
Complexity achieved by	Rare formation of new genes by chromosomal duplication	Frequent formation of new ideas and technologies

DISCUSSION

PEGGY BLATTNER (Albert Einstein College of Medicine, Bronx, New York): Would you comment upon the influence of prenatal environment and nutrition on these differences?

DR. MOTULSKY: Yes. Over the past few years, it has been shown again that nutrition may make a significant difference on postnatal achievement. The kind of poor nutrition that has been shown to produce severe impairment is usually not seen in our society. We need better definition of the type of nutrition that people get in our society, but malnutrition in our country probably cannot account for differences in achievement. I would look more strongly for postnatal environmental factors.

SECTION III

THE EFFECTS OF GENETIC COUNSELLING

Edmond A. Murphy

INTRODUCTION

As a subject for discussion, the effects of genetic counselling can be understood in three senses. First, how well does the consultand understand what the physician has said? Second, how big an impact does the genetic information have on the behavior of the consultands? Third, if certain reproductive policies were to be proposed and the consultands were to follow them, what would the impact be on the genetic composition of the population?

COMMUNICATION

In genetic counselling, the information which the geneticist is trying to convey to the consultands is of two kinds: biological and mathematical. The distinction, though of some value at an abstract level is nevertheless artificial. Part of the problem is to communicate the "facts of life" - what exactly goes on at meiosis; what the mechanism is by which the sex of the fetus is determined; in certain cases what is meant by the linkage and how it may help, for example, in antenatal diagnosis. The ability of the consultand to grasp this form of information will depend on his

intelligence and, also, on the familiarity he has with the ideas. The introduction of modern courses in biology at high school and in college has done much to help lay people to understand what is going on. The physicians with any real experience of having patiently explained a patient's condition to him is quite inured to hearing the most garbled version of his explanation at a later date. In the genetics clinic we certainly encounter the patient who has his facts hopelessly wrong - believing all his sons will inherit his hemophilia or that none of his children can inherit his Huntington's chorea. But the number of such gross misapprehensions is no greater than for any other piece of medical advice.

The other matter is a much more difficult one. Familiarity with a piece of knowledge may in many cases only create an illusion of understanding. Here, we could get into very deep waters, indeed. What exactly do numbers mean even to the scientist? Except for purposes of mathematical manipulation what does it mean to say that the radius of the visible universe is seven billion light years? Or that there are 10^{23} atoms in a glass of water? It is difficult to believe that there is much capacity for understanding or, at least, for testable understanding, in matters which are outside one's experience.

With genetic counselling, we are dealing with probabilities which, over and above those difficulties of understanding, also contain a quality of vagueness which is of no essence. Even trained probabilists have, in many cases, a poor enough grasp of the impact of a probability, however adept they may be at formal manipulations. It is commonly, and rightly, said that probability is the guide of life; it is also supposed that every respectable biologist lives with

probabilities. The correspondence between formal and pragmatic notions of probability, however, is not often established. In doing almost anything - crossing the road, taking a bath, drinking a cup of coffee - we take risks and do not become frozen into catatonia by the thought. Very few scientists, however, would have any accurate notion of the size of these risks which they take with such equanimity. The hiatus is aggravated in the case of the non-scientist.

It is probably the case that we make too much of the probabilities, perhaps because they are often more precisely known than the other material to be communicated. There is a widespread feeling that those who pursue the horses with stochastic interest acquire a practical feel for what is a reasonable set of odds to expect for taking a certain chance. But it seems to me that even a casual glance at the opulence of bookmakers and the poverty of the punter is sufficient to demonstrate that the odds are not equitable.

In thinking about probabilities, the layman always tends to confuse them with two things.

First, there is confusion between probabilities and expectations. If the risk of a disorder is 1 in 4, then the consultands planning to have four children expect to have one affected child. In the technical sense, this expectation is correct, but not in the lay sense. There is a tendency for them to believe that if under such circumstances they have two affected children, then they may expect compensatory good luck in the next few pregnancies. Of course, this is not so; indeed, quite the contrary. In many genetic counselling problems where the genotypes of the parents are not known with certainty, the outlook for the next child in the series is worse where there are two affected children than where

there is only one. For instance, in the case of an X-linked lethal, if we are confronted by a woman about whose family history nothing is known, the probability that her first son will be affected is 3μ where μ is the mutation rate. If her first son is affected, the probability that the next son will be affected is increased to one-third; if her first two sons are affected, the risk for the next son is further increased to one-half.[1] Where there is epistasis involved, the risk continues to rise progressively with each affected son.[2] Similar patterns are well known in traits believed to be multilocal: e.g. congenital heart disease.[3]

Then, secondly, probability tends to be mixed up - and perhaps rightly so - with cost. In the abstract, a risk of 1 in 10 means the same whatever the event of which it is predicated. But consider two situations where the parents are told that the risk of their next child being left-handed is 1 in 10; and where the risk of their next son being a murderer is 1 in 10. Parents would tend to dismiss the first risk as trivially small and the second as ominously large. Yet the same probabilities are involved.

Of course, it is sometimes necessary to call the attention of the parents to the fact that a rational basis for decision is not risk alone or cost alone.[4] Cost must, of course, be understood both literally and metaphorically: the nursing of the Duchenne form of muscular dystrophy is not merely economically demanding, it is also emotionally demanding both on the persons with the disease and on their relatives, with its long period of incapacitation and its relentlessly fatal outcome.

Three facets, then, must be communicated to the patient:

1. The intensity of the burden which is

imposed by the disease. In color blindness this is trivial at almost all ages; in the Lesch-Nyhan syndrome it is always severe.

2. The duration of the burden. This is brief in disorders which lead to spontaneous abortion of neonatal death. In hemophilia it extends throughout life which may be a long time. An unqualified reference to burden comprises both these notions: if we could construct a time-intensity chart, then the burden would be represented by the area under the curve.

3. The probability that the condition occurs. Dr. Chase will deal with this topic in some detail. What we call the expected burden is the product of the risk and the mean burden imposed by the disease.

I think it perhaps interesting to construct a rough table of disorders classifying them by three grades of severity; and cross-classifying them by three grades or risk or recurrence (Table 1).

A trait may be trivial on all counts such as left-handedness. It may be non-trivial but supportable either because, like tetralogy of Fallot, it has a low risk of recurrence or because though the risk is high the burden is slight, as in color blindness; or because, like congenital pyloric stenosis, it has a good prognosis and not a very high risk of recurrence. It is the disorders in the top left hand corner in which both the recurrence risk is high and the prognosis is poor, in which further reproduction should be undertaken with the greatest circum-spection. Going from top left to bottom right, then, the expected burden is declining. I think that the unsophisticated mind tends to travel along this diagonal rather than separately along the marginals; and this is, after all, perhaps the best strategy. The scientist, however, moves

with considerable security along the rows which involve, at least in principle, hard fact but much more uncertainly down the columns which involve value judgments.

The matter of how the consultands behave in the light of counselling is disposed of with embarrassing ease. Anecdotes abound: hard facts are at a premium. In the last year, Carter and his colleagues[5] have published an interesting report on a follow-up of consultands seen between 1952 and 1964. The objectives were threefold: to test understanding of advice, to find out what decisions the consultands made in the light of their understanding and to see how successful they were in carrying out their plans. In contrast to the foregoing, they dealt only with non-trivial conditions and the rest are classed by risk of recurrence. The treatment of understanding is sketchy. As to decisions, those at high risk were somewhat, though not strikingly, less disposed to have more children than those at low risk, though except for a few cases, it is not clear what concrete steps they took (Table 2). As to the number of further children per couple, this seems to have been a little lower in the high risk group: 0.60 compared with 0.91 in the low risk group. However, if comparisons are made within categories according to attitudes, the rates are much the same: if anything a little lower in the low risk group. It is unfortunate that the necessary brevity of the paper (it was published in The Lancet) meant excluding certain important details. For example, the ages of the consultands might be higher in the high risk group and, thus, they would have fewer subsequent children regardless of the genetic problem. A full publication of results would be welcomed in this arid area.

That is all I shall say about communication and

its impact. Dr. Chase is to discuss this whole problem both prospectively and retrospectively. I shall devote the rest of this communication to the impact of genetic counselling on the population as a whole. There are all manner of facets to this problem; I welcome the knowledge that we have other papers to deal with many of them. I shall consider it only as an evolutionary or, if you please, eugenic problem.

Motives underlying eugenics nicely illustrate the difference between society as a political unit and society as an aggregate of individuals. Harmful genes may impose their burden either through death or disease; mortality or morbidity. Death tends to be a private manner which society as a body does not mourn and about which it is comparatively little concerned. Death without sickness, as in car accidents, may prompt action if the scale of the problem is sufficiently massive; but causes which lead to prolonged incapacitation are much more likely to do so. More has been done about prevention of tuberculosis or coronary disease than about car safety or the avoidance of war.

Fund raising to study chronic disease has prospered whereas I can think of no instance of its being attempted for acute disease, however grave, or for national disasters which are usually left nonspecifically to the Red Cross.

This distinction is important to make at the outset. By eugenics we might hope to change mortality rates or morbidity rates and while the two are certainly not independent, neither are they interchangeable. It is easier to make general statements about the former, statements which are not colored by environment.

However, it is necessary to make a special comment on the nature of a death. In the ordinary sense, there is little difficulty in under-

standing what a death is; but a geneticist sees it in slightly different terms as the extinction of a genetic line. If a child is born with thanatophoric dwarfism and dies shortly thereafter, this is a death in the genetic, as well as the lay, sense. A man with Klinefelter's syndrome, and necessarily sterile, lives to the age of ninety and dies from cancer. He also is a genetic death but this notion might appear strange to a layman. Genetic deaths then are like the strange incident of the dog in the night;[6] they are reckoned not on what has happened but on what has not happened. We "call the roll" by considering average family size which we will denote by $\underline{Z}$ and since a couple who is sterile represent two genetic deaths, then a one-child family represents $\frac{2(Z-1)}{Z}$ deaths. The geneticist accepts the notions of fractions of a death which in the lay sense would be meaningless even if we do sometimes accuse our leaders of being half dead.

We have, then, three outcomes to consider: gene frequency, mortality and morbidity. They are all interrelated but to some extent separable.

Gene Frequency. We have four stages in the life cycle at which eugenic manipulations might operate: in the choice of mate, in the fertility of the couple, in the conduct of the pregnancy and in the medical care of the progeny. Changes in gene frequency depend ultimately, indeed tautologously, on the number of offspring of the various genotypes produced and the selection pressure to which they are exposed. To reach a final answer at the present time would be impossible because of unknown factors essentially of a cybernetic character. Chief of these is the unresolved dispute as to whether compensation occurs: if a couple lose a child because

of Tay-Sachs disease, does this discourage them from having further children? Or do they compensate and end up with the same family size? Or do they overcompensate and have larger than normal families? Reed[7] has a recent review of the subject. The question has not been answered even qualitatively and we would need to know the answer with some precision to make predictions. My own guess would be that so far, at least, the force of these feed-back-mechanisms would, on average, be small. Whether the widespread introduction of genetic counselling clinics and the increasing use of amniocentesis and other diagnostic measures will have any impact is another matter. Lacking the necessary facts, I can only ignore this facet of the problem and deal in terms of the fitness of a particular mating.

Most of genetic counselling is done to people who have already had affected children and, for example, Carter and associates in the study to which we have already referred[5] confined their attentions to this group. Nevertheless, there are at least some diseases (I think particularly of thalassemia, sickle cell anemia and Tay-Sachs disease) in which there are moves afoot to detect the heterozygotes among the unmarried and discourage them from marrying each other. Mass screening might, I suppose, be added to the list of impediments to the smooth course of true love which Shakespeare listed. Suppose, then, that we succeeded in preventing marriages between heterozygotes for one of these lethal autosomal recessive conditions. In this Symposium last year,[8] I showed what would happen to gene frequency when equilibrium is reached and, at some imtermediate stages, supposing a forward mutation rate of one in one hundred thousand and a back mutation rate of one in ten million. Since homo-

zygotes do not reproduce and heterozygotes do not marry, apart from new mutations, homozygotes will not occur. Thus, almost all of the outcome will depend on the selection against the heterozygotes. Should they be fitter than the wild type, we will have a balanced polymorphism on our hands, and then there is going to be a permanent toll of genetic deaths which pays for the extra fitness. But such instances are comparatively rare, in man at least, and usually the heterozygote will be less fit, though perhaps only slightly so. The net result, then, is that there will be an increase in the frequency of the gene until a new equilibrium is established. If the fitness is very close to unity the ultimate frequency may be high; but it is only when the fitness exceeds 0.99997 that the system will eventually break down because the heterozygotes outnumber the homozygotes and backcross mating is no longer possible. It would be extraordinarily difficult to detect such small losses of fitness so that for practical purposes, we would only run into difficulties with completely recessive conditions. I should say "ultimate difficulties", because, in fact, the rate of build-up of the gene frequency is extremely slow. Even in the heterozygous state if fully fit, after 20 generations, perhaps 500 years, the frequency of the gene has increased by only 5.9% over the equilibrium frequency under random mating. If the fitness is 0.9 then after the same interval the gene frequency would have increased by 0.07%. This scheme, then, would work very efficiently for autosomal recessive conditions. The disease would be virtually abolished and the cost would be minute loss of fitness on the part of the heterozygotes which could be attained by the very slightest reduction in mean family size. It would suppose a very efficient educational

program: marriage between heterozygotes would have to be censured by society with much the same pressure that is now directed against incest and, genetically speaking, for much the same reason.

Note that in the foregoing argument, I have dealt in terms of the frequency of the gene per unit of population. It, therefore, does not depend on whether or not the population size is fixed or increasing. It says nothing about the number of people that are carrying the harmful gene; but this does not matter, since the whole system depends for its efficacy on the ratio of wild-type to heterozygous mates available. Also, of course, the detection of the carrier state may be more or less involved and more or less expensive. In the broad view, I suppose we would want to deal with all harmful recessives simultaneously but this presents two difficulties. First, screening a hundred thousand loci (or whatever the figure is) in each prospective parent would be a formidable task; and, secondly, the more loci we considered, the more constraints there would be on choice of mate though this effect is not large. For instance, with a fitness for the heterozygote of 0.9, the equilibrium frequency of the gene under random mating would be about 180 per million and this is the frequency of the heterozygotes. This leaves the heterozygotes an initial choice of mates from 99.98% of the population. But suppose a person carries ten recessive lethals; his choice is now reduced to 99.8%. For completely recessive conditions the corresponding figures would be 99.3% and 93.87% respectively.

In large part, however, eugenic pressure will be exerted in couples already married, with an affected child. Two broad courses may be followed. The couples may decide to have no further children or they may be less inclined to

have them. This path is manipulating genetic fitness and, therefore, eugenically equivalent to the effects of medical care, a matter I shall deal with later. The other path is to proceed with pregnancies, to determine the phenotype of the fetus by amniocentesis and to abort fetuses of selected phenotypes. I shall not attempt to deal with the legal, philosophical or moral aspects of this strategy.

There are clearly circumstances in which it would not apply - for example, those who are opposed morally to abortion, of those who are unaware that some conditions can be diagnosed in utero. The genetic effects have been dealt with in some detail by Motulsky, Fraser and Felsenstein.[9] For definiteness, they suppose exact compensation, i.e. that couples will go on having pregnancies until they have a normal complement of healthy children. They provide figures on the extent to which screening, amniocentesis and abortion must be performed to obtain results in reducing the number of affected offspring. The ratio is high but not so high when economic factors are considered. The most efficient procedure is premarital screening which allows couples at risk to be detected and amniocentesis performed even in the first pregnancy. The scheme would, on the whole, be highly efficient for dominants where they can be diagnosed in utero: such is not the case for all but a few such conditions at the present time. As for recessives, the system would abolish homozygous cases who provide the immediate load; but since homozygotes are unfit and heterozygotes are not aborted, and the latter are the main repository of the genes, this would be a highly inefficient way of eliminating the ultimate load. Full compensation would tend to slow down elimination and if the mutation remains the same, the carrier

frequency would actually rise by approximately 20%. In evaluating these results, we must recognize that amniocentesis in not expert but average hands may carry a morbidity of its own. I know of no relevant data.

There is, of course, more to intrauterine diagnosis than selective abortion. It is possible that by this means we may be able to detect early, certain disorders which can be treated wither before birth or promptly afterwards. One thinks immediately of incompatibilities between maternal and fetal blood groups and a growing number of dietary disorders such as phenylketonuria, galactosemia, lactose intolerance and the like. I do not mean to imply that these disorders can all be diagnosed at present; but they are certainly conditions which we would like to diagnose.

The third and final way in which we may influence gene frequencies is by manipulation of the fitness of the individual. To recommend to a known or possible carrier of Huntington's chorea that he have no children would be such a measure. On a less drastic scale, we might recommend that he aim for fewer children than average. In such cases we would, in effect, be lowering the genetic fitness of the subject without otherwise influencing his well-being. The opposite measure would be to employ some treatment which would tend to relieve the selection pressure against less fit phenotypes. The impact on the gene pool in each case could be reduced to the same measure: what is the genetic fitness of such persons, that is, what is mean family size expressed as a multiple of mean family size in the wild type.

Suppose that at present the fitness of the dominant heterozygote or the recessive homozygote takes some arbitrary value; then assuming a fixed

mutation rate of 1 in 100,000 and a back mutation rate of 1 in 10,000,000 an equilibrium will be established. And if the fitness is changed, a new equilibrium will be set up. For dominant traits the new equilibrium is approached rapidly; for recessives, the new equilibrium is reached so slowly that there is little interest in knowing what the final values will be. It is best, then, to consider what will have happened after a certain number of generations. It is perhaps of very little interest to make prognostications a long way ahead, not because I mistrust the mathematics but because selection pressures cannot be expected to remain stable indefinitely. If we concentrate merely on the next 20 generations (or about 500 years), then an increase in fitness of a dominant to an arbitrary degree of fitness leads to an increase in gene frequency (Table 3). The greater the degree of fitness, the greater and more rapid the rise in frequency and the more slowly the increase levels off. If the fitness is less than 50%, the equilibrium frequency is reached more or less within five generations. For a dominant, of course, the case frequency is the gene frequency unless selection pressure is small. For the recessive, it is necessary to keep track of both the case frequency and the gene frequency. Even conferring complete fitness on what has hitherto been a lethal condition leads to a slow rise in gene frequency and an even slower rise in case frequency. The latter is 13% higher after twenty generations than it was at the start.

Mortality. The persistence of a gene in the population implies that the inflow of that gene from all sources (immigration, mutation or reproduction) must on average equal outflow (from emigration, back-mutation or death). So much is obvious; what is somewhat less obvious and

largely unknown to the propagandists is that the number of genetic deaths, defined in the sense given earlier, is not dependent on the fitness of the people who bear the gene but only on the mode of inheritance. This statement requires qualification. Strictly, it is true only if the population size is fixed. But the statement can be rescued if we deal not in the absolute number of deaths but in the sum of the deaths per unit of the population. This scaling seems sensible in any case because in considering any disease and its burden on society we always use this method: we do not argue that cancer is a bigger problem in the United States now than it was a hundred years ago because the population is much larger and, therefore, there are more people at risk. The implications of this assessment of the load of a mutation which for historical reasons we call the principle of Haldane[10] are that if we take three traits inherited in the same fashion, say the M blood group which is clinically not a disease, hemoglobin C which is mildly debilitating and achondroplasia which may be a serious burden, ultimately for each, one mutation causes one genetic death. For a detailed discussion, see Crow and Kimura, 1970.[11]

What is the theoretical justification for this statement? It has been shown extensively for all mating types by deterministic models, i.e. by supposing that the numbers of persons are so large that at each generation the actual numbers of the various genotypes will equal the expected number. Such methods have been used because they are simple to handle from a mathematical standpoint. They are, of course, unrealistic, but a more plausible stochastic treatment of the problem is much more demanding. Kimura has dealt with the behavior of such a gene using a diffusion approximation[12] and more recently at

least some of the results obtained have been shown to be approximately correct by Nei[13] who has carried through exact calculations. A stochastic solution to the problem in complete generality will be a much more formidable undertaking. Nei has shown, however, that under the stochastic model, the mean is the same as the result given by the deterministic.

From the eugenic point of view, the implication of this principle in a closed population is that the genetic burden reflects mutation and not fitness or the manipulations thereof. If we wish to abolish genetic disease, then we have to attack mutation, which I take to be environmental in origin. No amount of genetic manipulation will achieve the result. Genetic strategy, then, can only have the effect of redistributing the load. For example, it would be possible to eliminate sickle cell disease in one generation, by detecting the heterozygotes and sterilizing them. This has the effect of concentrating the accumulated load of the past in the 5% or so of carriers of this disorder; for all I know, this might be a splendid arrangement for the other 95%; but the minority might complain that, in a very literal sense, this is genocide. Also, of course, if we were to treat all carriers of lethal recessives in the same way, calculation shows that, at the most conservative estimate, 95% of the population would be sterilized. So much for the eugenic dream. The only sensible and humane course, to my mind, is to spread the load over a sufficiently wide segment of the population that nobody is confronted with an intolerable burden. Much in the same way we have insurance against disasters. The economic loss to the community remains the same whoever pays for it; but what might have been a crippling loss to one, becomes a small levy on many.

Morbidity is a very much more difficult problem to deal with in any generality. There is no firm rate of exchange between clinical or social fitness and genetic fitness. There is nothing contradictory in the statement that a habitual criminal or a leper is highly fit in a genetic sense. I say there is no firm relationship; nevertheless, I think it is likely that there is a good one. Treatment may have the effect of reducing the load of mortality at the expense of increasing the morbidity. But it is easy to exaggerate the risks. In the first place, the choice does not lie between pure mortality and pure morbidity. Those who die of genetic disease commonly go through a period of illness first; and I find it difficult to believe that the total morbidity from the homozogous state is not much greater than that from the heterozygous except for dominants in which homozygosity will be rare. This would surely be easy to test in selected diseases. There is certainly some morbidity associated with the sickle cell trait, but it is trivial compared with that from the homozygous. It would be difficult to think of a treatment which improves fitness in the genetic sense which did not involve proportionate improvement in the fitness in the clinical sense.

How much time and effort should be spent on the person with the disease is another question but is not a specifically genetic one. It is easy to lost one's sense of proportion; it is even easier to waste money and effort. Recently, a public health administrator protested after a lecture that it requires very elaborate and expensive hospitals to take care of children with cystic fibrosis and that if we let the gene become frequent we are merely multiplying this load. But he was unable to furnish me with any evidence that these elaborate and expensive hospitals did

anything whatsoever to the natural history of the condition, still less that it improved genetic fitness.

Then, secondly, we forget that the big problems are often easier to handle than the smaller ones. If everybody were sensitive to the fava bean, we would simply say that the fava bean is poisonous and there would be an end to the matter. It is because only a small number of people are affected by it that we call favism a disease at all. If ninety percent of the population could synthesize their own vitamin C, scurvy would be an inborn error of metabolism and not a deficiency disease. There is much talk about the perils of keeping the homozygotes for phenylketonuria alive; but if practically everybody were sensitive to phenylalanine, I am sure our economy would adjust to it easily enough. We can, of course, get into difficulties from a doctrinaire pursuit of statements which are only conditionally true. As Paige and associates pointed out,[14] the high percentage of Negroes with lactose intolerance belies the facile statement that milk is good for you, a principle which is doubtless true enough for the northern European population on which it is based. A little understanding of what is going on would make lactose intolerance a not insupportable burden on society. Here, as elsewhere, the propagandist would do well to look to his facts.

Then, thirdly, it is no trivial problem to decide which of two genes is harmful. There would, of course, be broad areas of agreement. Nobody wants to see more babies with anencephaly or adults with muscular dystrophies. There are, however, a great many cases in which the intrinsically subjective nature of these judgments is shown up, as in the excesses of those who believe that the good genes are confined to particular

racial groups. For my part, I take a pessimistic view of solving, by scientific means at least, the problems of what is normal and what is desirable. Normality in terms of survival value is much easier to formulate and to study than normality in a more subjective (though perhaps more worthwhile) sense. But "survival value" may be viewed under two aspects, survival of the mutant line and survival of the race. Hook,[15] if I understand him correctly, has expressed the view that there is quite enough genetic heterogeneity to be going on with and that he would be happy to see further mutation prevented. He may be right, though I should be a good deal more comfortable to see some kind of demonstration of the truth of this statement. But there seems to be little doubt that, even so, continued homogenization of a genetic stock is undesirable. It is not merely that we need diversity in the present situation (without variance, how would geneticists and statisticians make a living?). We also need a reserve of diversity to confront some drastic change in the environment. I, for one, would hate to put all my faith in our capacity to manipulate the milieu exterieur.

SUMMARY

It would take more arrogance than I could muster to decide what the ideal population of the future is like. Our main task is to deal not with perfections but with disease. There is a good reason to believe that the genetic load is environmental and while this is a major problem in its own right, I do not see it as a specifically genetic one. Given a fixed load the debt must be paid by somebody; and compassion seems to me to demand that we spread it as thinly as possible over the community. Much of what passes

for misfortune is the contrast between the lot of one and the lot of the other. The more evenly spread the load, the less distressing it is to anybody.

Protecting the individual family will, perhaps, inevitably lead to increase of frequency of harmful genes in the population. But the effect is slight and will probably only get out of hand when full fitness is conferred on the mutant genes; and if they are fully fit, then they will cease to be a genetic problem. What one can say about morbidity is much less secure. General experience would suggest that it tends to behave in much the same way as mortality; but more exact statements must await empirical studies.

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Table 1

A Classification of Genetic Burden

Average Burden	Risk of Recurrence		
	High	Intermediate	Low
High	Duchenne muscular dystrophy Tay-Sachs disease Hemophilia	Asthma Coronary disease	Tetralogy of Fallot Down's syndrome
Intermediate	Albinism Lactose intolerance Glucose-6-phosphate dehydrogenase deficiency	Congenital pyloric stenosis Gout	Hare lip Cleft palate
Low	Color blindness Kell negative blood group	Futcher's line Attached ear lobes	Left-handedness Somnambulism

Table 2

Subsequent Pregnancies to Consultands from a Genetics Clinic

(Data of Carter et al.,5)

	Number of Couples		Mean Number of Pregnancies
At high risk			
Deterred by risk	109	(64%)	0.26
Undeterred by risk	61	(36%)	1.21
Total	170	(100%)	0.60
At low risk			
Deterred by risk	60	(24%)	0.15
Undeterred by risk	191	(76%)	1.15
Total	251	(100%)	0.91

Table 3

Rate of Increase of a Harmful Gene under Relaxation of Selection
(Frequencies per million)

	Dominant Phenotypes				Recessive Phenotype	
Old Fitness:	0.00				0.00	
New Fitness:	0.50	0.75	0.90	1.00	1.00	
	Case Frequency				Case Frequency	Gene Frequency
Generation						
0	20	20	20	20	9.97	3157
5	39	66	94	120	10.29	3207
10	40	77	137	220	10.61	3257
15	40	79	163	320	10.93	3307
20	40	80	178	420	11.27	3357

Initial frequencies are based on a forward mutation rate of 1 in 100,000 and a back mutation rate of 1 in 10,000,000. Only fitness is changed.

THE BACKGROUND OF COUPLES WHO REQUEST GENETIC COUNSELLING

Gary A. Chase*

INTRODUCTION

Much publicity has been given to the important advances in fields related to genetic counselling such as prenatal diagnosis, carrier detection and the identification of individual chromosomes by staining techniques designed to elucidate fine structure. Several papers in the last few years have dealt with new methods for recording and keeping track of information in pedigrees for the purpose of genetic counselling. In the light of this new knowledge many are prone to forget that the communication of elegant results to the person requesting genetic counselling may be very ineffective. Little has been done to prepare the consultands to receive the type of information given by the counsellor, and there are few, if any, hard facts available about how much the typical married couple knows or understands of genetics, probability and the consequences in everyday living of the common genetic disorders.

It is clear that responsible and informed

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*Work supported in part by a grant from the National Foundation - March of Dimes.

decisions about the future childbearing of a couple are not possible without reliable and up-to-date information presented intelligibly. Genetics is one of those fields in which the intense interest of laymen does not seem to be reflected by an accurate command of the facts. Furthermore, it is often difficult to overcome in a short interview, misconceptions about heredity that may have been in the mind of a consultand for years.

The counsellor can perform effectively only if discussion is pitched at a level at which the consultands feel comfortable. There is no standard formula or list of statements that will work in every case; the approach which has the best chance of succeeding is that which takes into account the intellectual, social and psychological backgrounds of the couple receiving advice.

Should a future child be affected, it is essential that couples with a family history of genetic disease be informed of the modern treatment and of the current prognosis. The memory of misfortunes in past generations can leave a distorted impression in the minds of the consultands. This is especially true where significant advances have been made in the treatment of such genetic problems as phenylketonuria, and of such congenital malformations as cleft palate.

In planning future childbearing activities, the consultands and the counsellor should be aware of the attitude of the couple toward abortion, contraception, sterilization and adoption. The 25% risk of Tay-Sachs disease in an offspring of two carriers, with the possibility of accurate prenatal diagnosis, is a minor problem for most reform Jews but a significant one for the orthodox who on religious grounds may be opposed to abortion.

THE BACKGROUND OF CONSULTANDS

A few recent publications have dealt indirectly with the issue of how much interested consultands know about genetics before they make contact with a counsellor. Taylor and Merrill[1] reported on 21 families where the consultand couple had at least one son affected with Duchenne muscular dystrophy, transmitted as an X-linked recessive. The parents in these families generally had a high school education. In 12 of the 21 families the consulting parents were not able to answer correctly the question: "What is the probability that your next child will be affected with the same condition?" The authors are rightly concerned that such information was not successfully communicated to the parents during the course of diagnosis and prognosis. No mention was made by the authors of the well known procedure of carrier detection by assay for creatine phosphokinase.[2] This test does not allow complete discrimination between carrier and normal women but contributes information which may affect the odds markedly.

Sibinga and Friedman[3] investigated the parental understanding of concepts related to phenylketonuria (PKU). Their subjects were 40 mothers and 39 fathers of PKU offspring. These parents were exposed to discussions with their pediatrician concerning the nature of the disease and its genetic etiology. Also, they were given a standard pamphlet prepared by a manufacturer of a dietary product given to PKU children.

A simple questionnaire was administered containing items related to the genetic nature of PKU, the absence of a necessary enzyme, the fact that it is a metabolic disorder, the possible mental retardation of the patient, and the mode of treatment currently used. Only 19 percent

of the subjects showed comprehension of four or all five of these topics. Possibly the most important finding of these workers is that education seemed to convey no advantage in answering the questions, as judged by the accuracy of the subjects responses.

Leonard and her collaborators[4] have studied the relationship of educational background to genetic and general biological knowledge in 78 couples with one or more children affected by one of four diseases: PKU, Down's syndrome, cystic fibrosis and juvenile rheumatoid arthritis (the last disease was used as a non-genetic "control"). They found that in situations where the child's disease was of genetic etiology, there was a significant positive association between the number of years of education of the parents and their score on a questionnaire concerning knowledge of their child's disease.

Brown and his collaborators[5] studied the process of transmitting background knowledge of sickle cell anemia to medical, general and nursing students at an Ugandan university. A special introductory lecture covering the basic facts was followed by a question and answer session. Then, a questionnaire was answered by 139 students. Of these, 85% desired to be tested for the sickle trait; 80% would be concerned about the sickle status of their fiance if their own test was positive; 70% stated that their plans would be affected if they and their betrothed were both sicklers; and 75% gave a correct definition of the carrier state. These results are quite encouraging, although one must keep in mind that university students in Uganda presumably represent a minority selected for intelligence.

The counsellor cannot do an effective job unless

he is familiar with the cultural and educational background of the consultands and with their knowledge of genetics and probability. I have observed a counsellor who quoted a risk of 5 percent to an uneducated couple only to hear as a reply: "Does that mean we will have an affected child or does it mean we will not?" Such a response displays lack of basic understanding which must be remedied before communication of the details specific to the problem at hand.

It would be desirable to know beforehand how much people who might request genetic counselling know about genetics and probability and, secondly, what their attitudes are toward birth control, sterilization, abortion and adoption.

A PLANNED STUDY OF BACKGROUND KNOWLEDGE AND ATTITUDES

To begin the study of the first kind of knowledge, we are proposing to question young men and women now in high school. The study would attempt through interviews and questionnaires to explore five different areas:

1. Ability to grasp facts and principles
    a. Probabilistic reasoning
    b. General biology
    c. Mendelian genetics
2. Acquaintance with risks of everyday life
    a. Non-genetic
    b. Genetic
3. Mode of behavior in chance situations
4. Grasp of burden and utility
5. Background knowledge of the counselling process (e.g. whether the person has read about it in the lay press).

The relevance of the first category of knowledge is clear. There are some who are not really

capable of understanding that disease can be transmitted by genes from parent to child. In addition, belief that supernatural forces influence the sex and other phenotypic aspects of an unconceived child is widespread even in Western society. In a recently published paper in Nature[6] Pasachoff and his collaborators distributed questionnaires to two hundred male undergraduate students at Harvard University. They were asked to indicate their degree of belief in such items as flying saucers, astrology and extra-sensory perception. The subjects were told to indicate their degree of belief on a scale from zero to twenty, with zero indicating "total unqualified disbelief", ten indicating "neither belief nor disbelief", and twenty "total unqualified belief". The average score for the question "Do you believe in flying saucers?" was 8.0 among fourth-year students; that for the question "Do you believe in extra-sensory perception?" was 11.2 among fourth-year students. Of fourth-year biological science majors, 9.2 was the average score in response to the question "Do you believe in the power of prayer?" Similar questions will be put to our subjects.

The current tendency among some men and women in our society to take seriously predictions based on occult world-views will certainly have ramifications in the extent to which people will be in a logical frame of mind when they approach the counsellor.

The purpose of including questions in category 2 is to assess how aware the subjects are of the magnitude of the risks encountered in everyday life. For example, the risk of epilepsy (which is considered in most cases a non-genetic condition) in an unconceived child is of the order of 1 in 250. A couple who knows this will be in a good position to put into perspective a risk of

1 in 500 to an unconceived child of some condition which may be present in distant relatives. Many couples unaware of such "background risks" are unduly frightened and discouraged from having children.

Inquiry into the mode of behavior in situations involving risk is one of the greatest importance in predicting how a person will respond to genetic counselling. It will naturally be expected that those persons who take big risks in everyday life will not be deterred from taking a big risk of having an affected child. Areas of risk-taking which will be included are whether the person bets substantial sums of money and whether he drives at high speeds.

Fraser[7] cites an example of two women, the first of which had autosomal dominant bilateral retinoblastoma. With a 50% risk that her child would be affected she decided to become pregnant. The second woman had congenital unilateral retinoblastoma which, as was explained to her, was a developmental accident with little chance of recurrence. This woman declined to take the risk of having further children.

One is tempted to wonder whether a test could be constructed which would have been able to predict the reactions of these two consultands. Such a test would be of practical value because it would furnish the counsellor with a clue as to how the risk information should be presented. For example, suppose that during the procedure of counselling the woman with low-risk retinoblastoma, the counsellor had access to a test which indicated that the consultand was a highly cautious person. It would then be incumbent upon him to present the information in the most encouraging fashion consistent with the empiric knowledge.

A useful device for finding out how much a

person likes to take chances is the constant expected value bet. This situation can be presented as follows: you are offered two bets. In bet 1, the winnings will be one thousand dollars with a probability of one in a hundred; the loss will be one hundred dollars with a probability of one in ten; you break even eighty-nine percent of the time. In bet 2, the winnings will be one hundred dollars with a chance of one in ten; the loss will be one hundred dollars with a chance of one in ten; eighty percent of the time you break even. Both bets have an expected gain of zero. but the stakes are higher in the first bet. This technique was used by Charlotte Gilson in a doctoral dissertation.[8] She tested seventy-two high school seniors, half of whom were low achievers and the other half high achievers. The high achievers tended to prefer the higher staked bets. It will be interesting to see whether high achievement of the subjects in our study will be associated with the tendency to prefer a risky bet.

The consultand's concept of burden and utility is a key element in the process of deciding whether to have further children. Murphy[9] has commented that the burden of genetic disease can be concentrated in a high dose at one period of time (such as anencephaly) or can be spread out over life with no one period experiencing a large peak (such as albinism). A set of questions will be employed specifically to assess the subjects' preferences for high-intensity, short-duration burdens as apposed to the reverse.

A notion that has gained but little attention in past discussions of burden in genetic counselling, is the utility of further children to the couple requesting genetic counselling. It is difficult to resist the supposition that the social circumstances and number of existing

children of the couple have a major role in determining the extent of the desire to start or continue childbearing.

A typical question to be asked is: "If you were told that your next child would be affected with a severe physical handicap such as a congenital heart malformation, with a chance of one in ten, would you change your plans to have the child?" This line could be continued: "Would you want to have an abortion, if you were already pregnant and were given this risk figure?" And further, "Would the number of living children you already have influence your decision?"

The last category, that of background knowledge, is of interest in the light of the many articles that have appeared in popular magazines about genetic counselling and prenatal diagnosis. This last summer a patient was referred to our clinic under the impression that every genetic disorder could be diagnosed prenatally: she had apparently been led to believe this by her physician. She wanted amniocentesis and expected to find out whether her child would be normal. It will be of interest to learn whether the explosion of information in the popular press has been widely misinterpreted by the layman in the false hope that medical genetics can provide the perfect baby.

METHODOLOGICAL CONSIDERATIONS

A group of about one hundred 9th and 10th grade public school students with ages ranging from 14 to 17 has been selected for study. All of these students are currently (1971-1972) taking a year-long biology course with the same instructor. The students are divided into five sections which meet with the teacher at separate

times.

For a period of four to six weeks the students will be taught some basic genetics such as Mendelism, the nature and function of chromosomes, and elementary probability. Both before and after the instruction an attempt will be made to test their knowledge of genetics and some of their attitudes toward such situations as having a child affected with cystic fibrosis or Down's syndrome. The basic course material will be supplemented with specific information about various genetic disorders of man.

In cooperation with the teacher a list of questions will be assembled. The students will be tested before and after, but no questions will be given twice. Random selection will decide which questions are to be asked before and after the instruction period.

The questions will seek to assess both abstract and empirical knowledge and some attempt will be made to inquire as to attitude by asking questions such as "If you were told that there was a chance of 1 in 250 that your first child would have a major malformation of the heart requiring surgery and possibly long hospitalization, would you refrain from having children?" or "Which would you rather have (a) a child that is born dead or (b) a child that is physically healthy, but will never be smart enough to earn a living?"

The results of this study will be subjected to several levels of analysis of which the first is descriptive. It is valuable to have basic information on how many people believe in the supernatural, or how many would prefer a high risk to a low risk bet.

The next level of analysis is the comparison of attributes. It will be desirable to find whether in our sample certain classifications tend to be

associated, e.g. level of school performance and tendency to prefer a high-risk bet; propensity for high-risk behavior versus empiric and theoretical knowledge; knowledge of genetics and knowledge of empiric risk situations.

Since our sample includes children of varying racial and religious backgrounds, some effort will be directed toward the detection of possible characteristic differences in attitude among ethnic and religious groups.

Also, there is considerable variation between sections in school performance so that it may be possible to assess the relationship between general academic ability and ability to assimilate material related to human genetics.

The third level of analysis is the estimation of the parameters that may influence a subject's concepts of burden and utility in the context of genetic counselling. We shall try to define indices which will provide meaningful indications of how the subjects will behave in risk-laden situations such as those to be encountered in genetic counselling. We need to have a measure of how much people want children: perhaps there will be a set of questions that can discriminate effectively between those to whom having children is not of great importance and those to whom it is a crucial matter.

In interviewing the subjects in such a study as the one discussed here, it is important to be aware of the possible interaction between the interviewers and the subject. It is planned to select a small set of questions which will be asked of the same subjects by different interviewers in order to assess the effect of a change in interviewers. The questions will be altered in phrasing between interviews of the same subjects. A Latin square design can accomplish randomization and provide estimates

of the effect of the variant questionnaires, interviewers and the order in which the questionnaires are given.

Special caution must be observed in the interpretation of results from a study of high school students. There may be characteristic changes in attitude and knowledge which take place in the years between high school and parenthood. Also, the subjects in our study may find it hard to imagine themselves in the situation of being the father or mother of a genetically handicapped child and having to imagine what the change in their attitudes toward childbearing might be. We are planning to use some questions which are relevant to the student's daily experience. For example, in testing attitude toward the supernatural, we might ask: "If your mother dreamed that the bus you were riding in crashed, would you be afraid to ride the bus the next day?" In testing knowledge of probability, we might ask: "If two of your teachers had the name Smith and were not related, how would you explain the coincidence? Would your explanation hold up if both teachers were named Albrechtsberger?"

High school is the last exposure to formal education for many citizens of our society. It is hoped that students at this level have been prepared by their previous schooling and by their home environments to receive the kind of information essential to comprehand the prognoses given in genetic counselling. If, indeed, they are capable of learning this background information, incorporation of this material into biology curricula should be considered. If they are not capable of learning it, and if this finding is confirmed by other investigators, then the educational process should be examined so that we may learn how and at what time we can

best prepare future parents for their responsibilities to themselves and to the unborn.

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DISCUSSION

DR. MOTULSKY: I would like to make one comment regarding risk. In dealing with patients, it is important to differentiate between absolute and relative risk. Consider the following: you have a patient who is 25 years old and who gave birth to a child with Down's syndrome. The risk of having another child with regular trisomy 21 Down's syndrome is, let us say, one in one hundred. The random risk for a woman of 25 having a child with Down's syndrome is, perhaps, 1 in 3,000 or something of that sort. So, the relative risk of having a child with Down's syndrome for this woman is 30 times as high as that of someone who has not had a child with Down's syndrome. Now this sounds pretty bad if you tell just that to a patient but sometimes this is being done. Actually, what this woman is interested in is her risk of having a child with Down's syndrome. Assume the risk is one percent. The probability is 99% that she will not have a child with Down's, which puts quite a different view on her decision as against looking at a risk of 30 times greater than someone else. In counselling we should not use relative risks but absolute ones.

LAWRENCE SHAPIRO (Letchworth Village, Thiells, New York): Dr. Chase mentioned one problem with regard to whether genetic counselling has been a failure or a success. Take, for example, the lady with bilateral retinoblastoma: even though that woman decided to become pregnant despite the 50% risk, she was, in fact, a person who has had that disease herself and knows better than anyone what it represents to herself and to her family. So, the fact that she elected to have a pregnancy should not be interpreted as a failure in genetic

counselling.

DR. MURPHY: I quite agree with you. Dr. Carter's paper does not really draw a distinction between the understanding of the advice and the acting upon the advice. Somerset Maugham, I think, described a character who looked at everything, understood everything and was unimpressed. A great deal of genetic counselling is, perhaps, like this and that is why one should not treat genetic counselling as a black box. The only criterion of the result of our advice shouldn't be evaluated only in terms of reproduction. I think one should pay special attention to all possible outcomes and I think, in fact, in the study by Leonard and associates to which Dr. Chase referred, attention was given to these: What did people understand? What did they do about it? What was the result? These were regarded as three distinct outcomes.

DR. CHASE: I didn't mean to include that example as a failure of genetic counselling. I meant to include it merely as an example of the wide variability in behavior that one can encounter when presented with similar situations.

SECTION IV

SOME THOUGHTS CONCERNING THE DIRECTION AND INTENSITY OF NATURAL SELECTION WITH RESPECT TO HUMAN PHYSICAL HEALTH AND BEHAVIOR PATTERNS IN INDUSTRIAL WELFARE STATE DEMOCRACIES

Carl J. Bajema

Man's explosive increase in numbers throughout the world has greatly affected the delicate ecosystems of our planet and the organization of human societies. The forces set in motion by the rapid increase in human numbers that has already occurred will continue to alter ecosystems and will require adjustments on the part of human societies for generations to come even if mankind is successful in stabilizing the numbers of human beings living on this planet by the 1980's.

The changes in mortality and fertility patterns which led to the rapid worldwide increase in the numbers of the human species undoubtedly had genetic consequences (Kirk, 1968; Osborn, 1951, 1960, 1968; Bajema, 1971a, 1971b). Many societies appear to be on the verge of abandoning policies which favor continued population growth and adopting policies aimed at achieving a zero rate of population growth. The policies that a society adopts with respect to population size will have genetic as well as environmental consequences (Bajema, 1971a, 1971b). Human societies adapt to their environments genetically as well as culturally. Within

a society individuals vary with respect to their physical health patterns, their behavior patterns and their reproductive patterns (that is, vary with respect to the age at which they produce offspring (generation length) and the number of offspring they produce (fertility)). As long as differential reproduction occurs, the opportunity for change with respect to the frequencies of the genes underlying physical health and behavior patterns exists (Crow, 1958, 1961; Kirk, 1968).

The direction and size of the reproductive differentials in fertility and generation length determine the direction and intensity of natural selection. The rate at which genetic change takes place is a function of the genetic system involved in producing a particular health pattern or behavior pattern, and the degree of relationship that exists in a population between the specific genes an individual is carrying (his genotype) and the actual physical health or behavior pattern that he develops (his phenotype) as well as the intensity of natural selection - the size of the reproductive differentials.

I have briefly discussed the genetic implications of population control policies aimed at achieving continued population growth, population control policies aimed at achieving zero population growth by voluntary means, and population control policies aimed at achieving zero population growth by compulsory measures in an earlier paper (Bajema, 1971a). In this paper, I shall try to intelligently speculate about some of the consequences of past, present and future life styles in reproduction of citizens living in western industrial welfare state democracies.

The life styles in sexual behavior and reproduction appear to be changing in such a way in America and other industrial welfare state democracies that virtually all of the citizens of

these societies will be able to exercise complete control over the timing, spacing and number of children they have in the near future. These life styles in sexual behavior and reproduction will determine the size and the genetic make-up of future generations. Therefore, it is important that we evaluate the consequences of past and present trends and try to intelligently speculate concerning the probable consequences of projecting these trends into the future. Only then will we be able to determine the severity of the problem and determine what steps, if any, need to be taken to regulate population size and to maintain or improve the genetic heritage of future generations.

There is evidence that supports the contention that if contemporary industrial societies were to allow their citizens to have complete and relatively free access to the means by which they can control their fertility, the resulting fertility patterns will lead to zero or even negative population growth. Childbearing patterns have developed which are below replacement level in Hungary and Japan where abortion has been essentially available to any woman who requests termination of pregnancy during the first three months of gestation. Sweden, which provides its citizens with adequate education with respect to contraception and relatively free access to contraceptives, has had childbearing patterns which have been below replacement level for more than a generation. (Bernhardt, 1971; see Population Reference Bureau, 1970, for a description of Sweden's population policies.)

What will be the genetic consequences of the childbearing patterns which are developing in western industrial welfare state democracies? Will they bring about the genetic twilight of western man? Will these childbearing patterns

bring about a decrease in the frequency of those genes in human populations which, upon interaction with the environment, lead to the development of health patterns and behavior patterns that enable individuals to successfully cope with the challenges of their environments and to take full advantage of the opportunities for self-fulfillment present in society?

NATURAL SELECTION AND PHYSICAL HEALTH

The evidence seems to clearly indicate that the frequencies of those genes which cause poor physical development and/or poor health in the absence of specific medical therapy have been increasing in human populations as a consequence of advances in medical treatment which reduce the intensity of the adverse phenotypic effects that the carriers of these genes have to cope with. The development of specific medical techniques which alleviate the harmful phenotypic expression of numerous rare genotypes such as hemophilia, phenylketonuria and pyloric stenosis, allowing these individuals to survive in greater numbers to adulthood has raised the specter of the genetic twilight of man with respect to his physical health (Muller, 1959, 1967). That this is not an immediate threat has been pointed out by other speakers at the Symposium today. All societies have to cope with a continual input of harmful genes into their population via mutation. The genetic status quo can be maintained in a population only if the number of new mutant genes being added to the population is counterbalanced by an equal number of new mutant genes not being passed on due to the nonreproduction or decreased reproduction of individuals carrying these mutant genes. Otherwise, the proportion of harmful genes in the population will increase.

The genetic heritage of human populations could be maintained or improved only if a significant number of individuals carrying harmful genes refrain from having children or utilize artificial insemination and/or artificial inovulation (when it becomes available) when having children. This could be accomplished, in part, if heredity counsellors would routinely discuss all the alternative solutions including artificial insemination and/or artificial inovulation with prospective parents who face a risk greater than 1 in 10 that any child they have will be seriously genetically handicapped. The long term loss in individual freedom by human beings yet unborn who, as a consequence of contemporary dysgenic life styles in reproduction, are genetically handicapped cannot be taken lightly by those individuals involved in heredity counselling nor by the prospective parents when they are informed of the genetic risks involved.

The genetic effects of specific medical therapy, heredity counselling, prenatal diagnosis and eugenic abortion have been discussed in some detail by other speakers at the Symposium today. The genetic consequences of heredity counselling coupled with mass prenatal genetic screening programs and the availability of eugenic abortion could have the effect of making the current dysgenic pattern of births present in welfare state democracies less dysgenic and possibly eugenic with respect to physical health in the near future.

NATURAL SELECTION AND BEHAVIOR

The selective forces operating with respect to human personality patterns in industrial welfare state democracies have changed during the past generation. For instance, the fertility of

schizophrenics and other individuals who have been admitted to hospitals for the mentally ill have increased relative to the rest of the population (Erlenmeyer-Kimling and Paradowski, 1966; Erlenmeyer-Kimling, Nicol, Rainer and Deming, 1969; Shearer, Cain, Finch and Davidson, 1968; Stevens, 1969a, 1969b). This increase in the fertility of mentally ill individuals appears to have been due in part to the development of tranquilizing and other drugs and community-oriented psychiatric treatment which has decreased the length of stay in the hospital and, in part, to the trend toward a younger age at marriage and childbearing throughout the general population which has increased the probability that schizophrenics and other mentally ill individuals will marry and reproduce before the age at which grossly abnormal behavior patterns develop. Erlenmeyer-Kimling and Paradowski (1966) found that the fertility of schizophrenic women increased from 60% of that of comparably aged women in the population for schizophrenic women admitted to New York State hospitals in the years 1934-36 to nearly 90% of that of comparably aged women in the general population for schizophrenic women admitted to New York State hospitals in the years 1954-56. Thus, selection against individuals who develop behavior patterns which are aberrant enough to bring about hospitalization appears to have been relaxed during the past generation. Virtually nothing is known about the direction and intensity of natural selection with respect to human personality patterns in the general population. Muller (1960, 1967), Hardin (1968), Mayr (1961) and most others who have attempted to predict the probable effect that the socioeconomic and cultural environments of a welfare state democracy would have on man's genetic make-up have concluded that natural

selection would favor those personality patterns that most people consider least desirable.

Dire predictions were made a generation ago concerning the genetic consequences of the then existing childbearing patterns in industrial welfare state democracies particularly with respect to the genes underlying behavioral patterns such as intelligence (Cattell, 1937; Burt, 1946; Cook, 1951; etc.). The earliest attempts to quantitatively estimate the direction and intensity of natural selection with respect to individual differences in intelligence (as measured by IQ) involved ascertaining the relationship between the IQ test performance of school children and the size of the families from which these children came (number of siblings or the size of the families of origin). These studies (Cattell, 1937; Roberts, 1941; Burt, 1946; etc.) consistently found that the correlation coefficient between IQ and size of family of origin was negative and ranged from -0.12 to -0.46 with the median of the studies at -0.25 (Waller, 1969). The consistent finding of a negative correlation between IQ and size of family origin coupled with data from census reports and other studies which found inverse relationships between fertility and such factors as socioeconomic class, education and income led many demographers and geneticists to believe that this pattern of births was an inevitable concomitant of the industrial welfare state society and would lead to genetic deterioration of the human populations living in these societies.

Changes in the life styles in reproduction of Americans with respect to characteristics such as educational attainment, occupation and income which are positively correlated with mental ability indicate that the selective forces operating with respect to human intelligence have

changed in the United States during the past generation. Group differences in fertility with respect to educational attainment, occupation and income have decreased quite dramatically during the past several decades (Kiser, Grabill and Campbell, 1968; Cho, Grabill and Bogue, 1970). For instance, the completed fertility of married women with four or more years of college has increased from 59 percent of the average for all married women born 1901-1905 to 73 percent for all the women born 1916-1920 and should rise still further to approximately 90 percent for the women born 1926-1930 who are just completing their childbearing years (Kirk, 1968).

Three studies of the direction and intensity of natural selection in relation to individual differences with respect to human intelligence were conducted in different regions in the United States during the 1960's (Kalamazoo Fertility Study, Bajema, 1963, 1966, 1968; Minnesota Mental Retardation Study, originally carried out by Reed and Reed, 1965 and updated and reanalyzed by Waller, 1971; Third Harvard Growth Study, Bajema, 1971). These three studies are based on samples of individuals who were given tests as school children, who constituted a cohort of Americans most of whom were born between 1915 and 1920, and who are quite representative of many American populations.* In all three studies, the

*The Kalamazoo Fertility Study and the Third Harvard Growth Study were based on white, native-born Americans who were raised in urban environments while the Minnesota Mental Retardation Study sample was based on white native-born Americans, some of whom were raised in urban environments and some of whom were raised in rural environments.

traditional negative correlation coefficient between the IQ of an individual and the number of his (or her) siblings was observed (Table 1). In the same three studies the correlation coefficient between the IQ of the individual and his (or her) subsequent completed fertility was observed to be slightly positive (Table 1). In all three studies, the individuals with the highest IQ's (IQ > 130) produced more offspring on the average than did the individuals with lower IQ's (Osborn and Bajema, 1971). The positive relationship between IQ and subsequent fertility observed in these three studies indicates that for many of America's populations (mainly urban in upbringing, white, native-born) during the period of time in history of the 1930's to the 1960's (the reproductive years of the three study populations) natural selection was operating to bring about a very slight increase in the frequency of the genes which interacting with the environment result in the development of above average intelligence.

The consistent finding of a negative relationship between the IQ's of individuals and the number of siblings they have in all three of these studies coupled with the consistent finding of a positive relationship between the IQ's of the same individuals and their subsequent completed fertility (number of offspring) in the same three studies emphasizes two facts that every geneticist and demographer needs to be reminded of. First, any study of fertility which uses the number of siblings an individual has to estimate the differential fertility omits the nonreproductive proportion of the population. The nonreproductive group may comprise up to 20 percent or more of the population and cannot be assumed to be a random sample of the population. With respect to IQ, all three of the above

mentioned studies found that the probability that an individual would not produce any offspring was inversely correlated with the IQ of the individual. Many very important sociological studies of differential fertility often exclude separated, divorced and widowed individuals as well as non-married individuals from their samples. Therefore, demographers and geneticists should be very cautious with respect to utilizing such potentially biased data to predict the genetic consequences of the life styles in reproduction of a particular birth cohort. Second, the direction and intensity of natural selection with respect to a behavior pattern such as intelligence is a function of many social practices prevailing at any particular time. Therefore, it is important to project how the changes that are taking place in the social structure of society may affect life styles in reproduction if one is to intelligently speculate concerning the future direction and intensity of natural selection with respect to such a behavior pattern as intelligence.

PROJECTION OF TRENDS WITH RESPECT TO GROUP DIFFERENCES IN FERTILITY RELATED TO HUMAN BEHAVIOR PATTERNS

There is some evidence which when taken collectively indicates that the negative group fertility differentials with respect to such characteristics as educational attainment, occupation and income in America may disappear completely and that a slightly positive relationship may even develop in the future. The studies of Goldberg (1959, 1960, 1965), Freedman and Slesinger (1961) and Duncan (1965) have shown that in the United States the classic relationship between fertility and income, occupation and

educational attainment in urban areas was produced almost completely by the individuals who were raised in rural environments and migrated to the cities. While most of these individuals lacked the formal education and occupational skills necessary to enter high paying, high status urban occupations they did bring their high rural fertility norms with them when they migrated to the cities. As the proportion of the American urban population that was raised in a rural environment decreases the urban fertility differentials can be expected to change in a positive direction.

The proportion of Americans who exercise virtually complete control over their childbearing is increasing very rapidly. As American society gets closer and closer to its goal of "Every Child a Wanted Child" ("Babies by Choice - Not by Accident") group fertility differentials can be expected to change in a positive direction. Evidence from three studies supports this contention.

First, the Indianapolis Study (Kiser and Whelpton, 1949) found that among fecund couples who were successful with respect to planning their families, there was a small positive correlation between socioeconomic status and childbearing. Second, the 1965 National Fertility Study (Bumpass and Westoff, 1970, Ryder and Westoff, 1971) ascertained group differentials with respect to births which were unwanted at time of conception during the early 1960's in the U.S.A. and found that a strong inverse relationship existed between unwanted births and the mother's educational attainment as well as the family income. One would project on the basis of these two studies that as more and more Americans were allowed access to the means by which they can more effectively control their childbearing

group differentials with respect to fertility would shift in a positive direction. Third, evidence exists which suggests that an increase in the age at marriage may well have the effect of also making group differentials in fertility change toward a more positive relationship (Bumpass, 1969). More effective control over childbearing via contraception and abortion will also probably decrease the number of early marriages (especially teenage marriages) many of which are contracted to legitimatize a pregnancy.

The changing status of women will undoubtedly affect differential fertility. The increased educational opportunities for women should bring about an increase in assortative marriages for educational attainment (Eckland, 1970, 1971). Kiser, Grabill and Campbell (1968) and Kiser (1968) found that positive assortative marriages for educational attainment among women age 35-44 years who attended college had the effect of increasing the fertility of these women. Garrison, Anderson and Reed (1968) found that positively assortative marriages for educational attainment produced more children than negative assortative marriages.

The effect that increased occupational opportunities and job-security (including maternity leaves) for women has on differential fertility is very difficult to determine. Fertility rates are conspicuously lower for women in the labor force than for those not in the labor force. However, the effect that employment of the woman outside the home will have on differential fertility is not at all clear. Needed social reforms such as the provision of free or low cost high quality day care nurseries for preschool children and vacation day care recreational and educational programs for school age children should have an effect on differential fertility

in addition to enhancing the phenotypic expression of the genetic potentialities of the children participating in such programs. Research is needed to determine what the effect of such a reform might be on the childbearing patterns of populations.

As the social benefits of having large families decrease and the economic costs of raising children are more clearly perceived, fertility may very well become positively correlated with income. Income is correlated with various abilities and one would expect the frequency of the genes underlying such behavior patterns to increase if fertility is positively correlated with income. This is exactly what appears to be happening in West European industrial welfare state democracies (Bernhardt, 1971; Tobah, 1971).

Group differentials in fertility with respect to education, occupation and income are becoming more important in terms of their genetic consequences because of America's political policy of equality of educational and occupational opportunity based on ability. The GI Bill with its dependency allowances, other scholarships and graduate fellowships (occasionally with dependency allowances also), the establishment of community colleges and other regional institutions of higher learning, the provision of low cost loans for students attending college and other social reforms have increased the social mobility of able individuals coming from poor socioeconomic backgrounds. This policy of equality of education and occupational opportunity based on ability has been so successful that it is reducing the within (intra) group variation (Turnbull, 1968). This also has the effect of increasing the variance with respect to IQ in the population thus increasing the opportunity for natural selection (Eckland, 1969).

However, the genetic variation within educational attainment, occupational and income groups is still so great that one has to be extremely cautious in making conclusions concerning the genetic consequences of differentials in fertility if only group differentials are studied. Nonetheless, the continuing evolution of industrial welfare state democracies toward the meritocracy where individual status is based more on one's ability and achievement rather than on the socioeconomic status of one's parents will make group differentials in fertility with respect to educational attainment, occupational status and income more meaningful in terms of their genetic consequences with respect to human behavior patterns.

CONCLUSION

The direction and intensity of natural selection with respect to human physical health and behavior patterns is a function of many social practices prevailing in a society at any particular time. An attempt was made in this paper to begin to project how the changes that are taking place in the social structure of industrial welfare state democracies may affect the direction and intensity of natural selection with respect to human physical health and behavior patterns.

Western industrial state democracies are in the process of abandoming their pronatalistic policies and practices and moving rapidly toward establishing "Every Child a Wanted Child" policies and practices which allow individual citizens to exercise complete control over their fertility. These ongoing changes in the social institutions of societies affect life styles in reproduction and, thus, have been, are and will

continue to alter the direction and intensity of natural selection particularly with respect to human behavior patterns in addition to affecting population size.

The tremendous changes that have and still are taking place with respect to the role of children in society undoubtedly affect individual decisions that citizens of industrial societies make concerning how many children they will have. As Norman Ryder (1969) has pointed out:

"A convincing case can be made that the economic development of the West required assertion of the primacy of the individual over the family, and that this was the essential basis for modern fertility regulation. Society intervened on behalf of the individual to top the balance of power; the worker against the owner, the woman against the man, and the child against the parent...In the West societies slowly but inexorably took the side of the child against the parent, specifically enforcing compulsory education for a progressively longer time span, delaying more and more the entry of the child into the labor force, and establishing the claim of the child as worker over the fruits of his own labor. The core of the solution of the problem of fertility regulation is implementation of a declaration of the rights of children. This is indeed revolutionary: what is required is a reversal of the entire temporal direction of obligation from what the child owes the parent to what the parent owes the child."

It is no longer in the selfish economic interest of the citizen living in an industrial society to have children (Miles, 1970). Today, children are economic and time consuming liabilities even in industrial welfare state societies which subsidize some of the financial costs of bearing and raising children, and which

by providing universal education make it possible for parents to have short periods of time almost every day when they are free of their child-rearing responsibilities. This should mean that individual decisions to have children will become more and more based on what Berelson (1971) has called the "consideration of the welfare of the child in the richest sense of that term and thus by extension to the next generation(s)." In other words, decisions concerning childbearing should become based more and more on the right of individuals yet unborn to be as free from genetic handicaps as possible and to be able to live in as high quality environment as possible.

Evidence has been presented in this paper which supports the contention that the completion of the above social and economic changes with respect to freedom of parenthood and the role of children in society should result in life styles in reproduction that are at or below replacement level with respect to population size and that are eugenic with respect to the genetic heritage of future generations.

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Table 1

NATURAL SELECTION IN RELATION TO HUMAN INTELLIGENCE
Correlation Between Intelligence (as Measured by IQ) and
(1) Size of Family of Origin (Number of Siblings)
(2) Subsequent Completed Fertility (Number of Offspring)
in Three American Studies

Study	Sample Size	Correlation Coefficient $r_{IQ\ Sibs}$	Correlation Coefficient $r_{IQ\ Offspring}$
Minnesota Mental Retardation Study	713	-0.12	+0.11[a]
Kalamazoo Fertility Study (Bajema, 1963)	979	-0.26	+0.05[b]
Third Harvard Growth Study	1,533	-0.25	+0.04[b]

[a]At age 40 or time of death, if before age 40.

[b]At age 45 or time of death, if before age 45.

(Taken from Bajema 1971c)

GENETIC IMPLICATIONS OF ABORTION

Ernest B. Hook

A large number of ethical and social questions have been raised concerning abortion. Some of these concern abortions done because the fetus has a genetic disease. What will loss of such individuals do to the gene pool, and will this have an eventual deleterious effect upon the viability and general health of the population? A conclusion here is somewhat uncertain, unless we know how many children a mother will have after she has lost a diseased fetus. Presumably she has undergone an abortion not because she doesn't want children but because she does, but healthy ones unaffected by disease. Thus,it is not unreasonable to assume that such a mother, if known to be at risk before her first child is born will ultimately have about as many children as an "average" mother who has not undergone such a procedure. But, if discovered to be at risk after the birth of an affected child, she might have even more than this average figure, particularly if the affected child has died or has been institutionalized.

Since the precise population outcome will depend upon these as well as a large number of other factors (e.g. genetic fitness of affected individuals, genetic fitness of carriers, change of fitness with social and medical changes, etc.) this discussion will be restricted to a qualitative discussion of possible outcomes. Given any

reasonable assumptions concerning reproductive compensation and fitness, the practical implications of the changes in gene frequency are likely to be of the same significance. (Precise calculations of population changes as a function of various parameters of different genetic diseases have been published by Motulsky et al.[1])

We may distinguish types of outcomes by the mode of inheritance of the condition involved. If the disease in question is a genetic dominant then a decrease in the disease will be paralleled by a decrease in gene frequency and there is no reason to think this change will have deleterious consequences.

The situation is more complicated with regard to recessive disorders since under some circumstances the gene frequency will go up and in others it will decline. Indeed, the theoretical eventual upper limit is around 50% carriers in the population if therapeutic abortions are done on all affected fetuses, there is some carrier advantage, and the disease is not presently at equilibrium but already increasing in frequency.

However, the main point to be made is that from a practical point of view a significant change in gene frequency due to abortions would take a great number of generations to occur. The rate of change would be exceedingly small under any reasonable assumptions concerning carrier advantage and family size. The reason for this simply is that carriers rather than diseased individuals account for the vast bulk of the disease alleles already in the population. For instance, for cystic fibrosis, a relatively common disease, at birth there are about 80 times more carriers than affected. For rarer diseases, such as phenylketonuria, the ratio is higher (perhaps 125 to 150 more carriers than affected for PKU). For such disorders thus only about 1-3% of the total gene

frequency are accounted for by diseased individuals. Replacement of these individuals in part by carriers is likely to have a relatively small effect upon the gene frequency in the next few generations.

The situation for X-linked disorders is more complicated since affected individuals account for a larger proportion of the genes in any generation than for recessive disorders. There would thus be an increased rate of loss of the genes due to abortion. But replacement of affected males in part by carrier females will also be more rapid however, and tend to produce a change in the other direction. Thus, these factors would tend to negate each other and the net effect on gene frequency is also likely to be relatively gradual.

Similar considerations apply to the incidence of translocations that produce Down's syndrome (mongolism), for instance. The incidence of such carriers is very low now, probably less than 1/10,000 to 1/20,000, so replacement of translocation mongoloid offspring in part by translocation carriers will not have a striking effect upon the frequency of this translocation in the population at large, or the incidence of all mongoloid fetuses in the next generation. In addition, we have no evidence to date to suggest that loss of the more frequent trisomy mongoloid fetuses by older mothers and replacement with normal individuals will have any significant effect upon the incidence of such trisomy 21 fetuses in the next generation.

In all these situations, as well as those involving gross congenital malformations if they could be diagnosed prenatally, the effect upon the incidence of <u>disease</u> frequency at birth will be dramatic, occurring in one generation if all individuals at risk undergo the procedure. The

effect upon the frequency of whatever genes (or translocations) may be involved however, will be very small and not as rapidly changing (with the exception of dominants). So these procedures would have to be done every generation for a long period.

These considerations apply only to abortions done because of disease in the fetus.* But the vast bulk of abortions done at present and probably those well into the foreseeable future are not performed because the mother wants healthy children but because she doesn't want any at all at the time of the procedure. (About 200,000 abortions had been done in New York State in the first year after repeal of the legal sanctions of this procedure; perhaps only a few dozen of these were done because the fetus had a genetic disease.) It cannot be stated absolutely that these frequent abortions will have no effect on the gene structure over a long period, but it is likely that the fetuses aborted represent a sample genetically similar to those who survive to birth for the most part, so the effect, if any, will probably be very small in each generation. (This assumes that the abortions are proportionately distributed among genetic sub-groups within the entire population. But even if this were not the case, the overall effect on genetic

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*Should abortions be done on any significant scale upon fetuses that are only carriers of recessive disorders then a very dramatic fall in frequency of the genes involved would be likely in one generation. But this seems very unlikely to occur, given current social conditions, since it would mean that families wanting healthy children would be consenting to procedures leading to loss of phenotypically normal fetuses.

structure would be likely to be the same as if there were such differentials only in family planning and/or birth control.)

Thus, from a practical point of view, the whole question of the effects of abortion upon gene frequency or genetic structure of the population are irrelevant to our other social and ethical concerns with this procedure in the next few generations.

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DISCUSSION

DR. CHASE: It is probably true that most abortions are not undertaken for the purpose of eliminating a gene with a deleterious effect. We should take this into consideration when we make generalizations about abortion. There is no evidence that either abortion-on-demand or contraception-on-demand is eugenic. Abortion on demand may be dysgenic. I don't know. We read in the press that every child should be a wanted child. This is fine but, unfortunately, some fetuses are not permitted the opportunity to become a wanted child because they have been the victim of an abortion. I think that we should look at this idea in another way: namely, every person should be a person respectful of life and consider the possibility that life might deviate from perfection. This would then allow less than perfect children the opportunity of developing their potential as human beings.

ELLYN STECKER (Toronto General Hospital, Toronto, Canada): Dr. Bajema, what effect will the changing status of men have on fertility rates?

DR. BAJEMA: I feel that childbearing can become a more and more altruistic function in our society. It's going to become more and more difficult for us to exploit children. And because it is going to become more and more difficult to exploit them, I think there is a greater possibility that we are going to have children for the right reasons.

The comment was made that every child should be a wanted child. I think you have problems when you start insisting that every child be a wanted one. If you have problems with the implemen-

tation of that particular goal, I'd like to know where you draw the line in your direction.

DR. CHASE: I guess if I had to draw a line, I'd draw it at conception. I'm not trying to push my point of view. I'm saying that a line is drawn by everybody and that it is important to keep this in mind.

DR. BAJEMA: The problem with some of the people involved in genetic counselling is that they wish to force their particular view on the parents, or prospective parents, by denying information concerning alternatives. How many genetic counsellors discuss the possibility of artificial insemination or eugenic abortion? I'm not asking whether or not they like it: that is irrelevant. I think every prospective parent has the right to know the available possibilities and be allowed to base their choice on their beliefs. The beliefs of the counsellor are not relevant. Physicians and genetic counsellors are not guardians of the morality of the people.

LAWRENCE SHAPIRO (Letchworth Village, Thiells, New York): I'm a genetic counsellor and I don't fancy myself as such a guardian of morality. However, to discuss artificial insemination or adoption once genetic counselling has been given, without having the couple raise the issue, in a sense, forces one's views on them. Once the counselling has been undertaken, then it's appropriate to discuss these possibilities. This is often not the situation.

DR. BAJEMA: I didn't say anything about offering them the alternative. I said discuss. And I think that's a big difference. Human beings ought to be given the opportunity to know

what all of the options are and then act on them. I think a heredity counsellor who keeps prospective parents in the dark with respect to some of the options is being unethical. I'm not saying one has to force the option upon parents. We've been talking here about being as objective as possible with respect to giving an accurate description of the risks involved. Let's do the same thing with respect to choices.

DR. SHAPIRO: That's fine, I don't disagree with that. But in practice it doesn't work that way. We've heard many people tell how the presentation of risk figures can be easily misunderstood, even a simple description of one-in-four risk. Despite the fact that the discussion may be comprehensive, it may require staging. There may be one, two, three or even four meetings with a particular family, just to get them to understand what the simple risks are. I think that it's too easy to say that all the alternatives should be extensively discussed: it's just not always practicable.

DR. ADAMS: I have, on occasion, as I am sure many of you have, consulted a lawyer for knowledge or guidance in making a decision. In other words, I have paid to have expert advice. I also don't completely skirt the issue of giving some advice when I think it's appropriate but sometimes it's impossible to convey all the information completely to my patients. I think it's a wonderful desire to try and educate everyone you see in genetic counselling but, of course, it is often difficult and not always possible.

DR. MURPHY: I can agree in principle, but the only completely moral choice anybody can make is

the completely informed moral choice. However, I think it is extraordinarily difficult in any situation to cultivate precisely the kind of neutrality that one would like. It is difficult to present to somebody, in a completely dispassionate way, all the possible alternatives. Anybody who is accustomed to giving medical advice - who is accustomed to seeing patients in any clinical situation - is familiar with this problem. There is no point in trying to scare the patient into doing something that he does not want to do. I think the psychiatrists, for instance, are fully aware of this particular phenomenon. Ultimately, a person must solve his own problems and make his own choice. But, there is an obligation on the part of the person who is doing the counselling to be fully informed about the pertinent facts and ideas.

DR. HOOK: Dr. Gordon, as I understand it, you will have absolutely nothing to do with abortion even if the patient who consults you is at high risk. What would you do if you were counselling a 21-translocation carrier early in pregnancy? Would you withhold the information that she could, in fact, avoid having an affected child, refer her to another center where this information could be presented to her or would you take some other course?

DR. GORDON: I have no truck with abortions under any circumstances. If the referring physician raises the question of amniocentesis or if the patient herself raises the question of amniocentesis, I say to them that I have no truck with amniocentesis and abortion but should either be requested, I can readily refer them to someone else who would be in a position to discuss this with you.

DR. HOOK: Suppose she does not raise the question?

DR. GORDON: Then I don't raise it. I will say to the woman (if she is a translocation carrier) that there is an 80 percent chance that her baby will not have Down's anomaly and that's where I leave the matter. I certainly do not put it to the mother that she might think in terms of destroying her baby. Not at all. But, if the matter is raised with me, I would certainly say to them that although I, myself, for my own reasons (and I don't necessarily need to explain them) do not take part in this kind of procedure, I will be perfectly satisfied to refer them to someone that will.

DR. STECKER: If you do have a woman at high risk of having a mongol or other genetic disease for whom abortion is not an acceptable choice, what do you offer her as an alternative? Should she have a baby? Do you discuss the possibility for taking care of this child? As you know, it is not just a matter of "you can keep it at home or put it in an institution".

DR. GORDON: The situation that you refer to is a much more common and vastly more important one than the one raised by Dr. Hook because this is the sort of thing that I am faced with frequently. Now, to answer your question, let me cite the last patient I saw for genetic counselling before coming here.

It was really an appalling situation and, I think, it highlights the very questions that you ask. This is a young woman, a nurse in a psychiatric hospital. She is in direct line of descent of a family with a history of Huntington's chorea. She knows as much as I do about the

genetics of Huntington's chorea and she probably knows more than I do about the day-to-day implications. She doesn't want to have another child. Her husband insists that she does. I discussed it with both of them and she says that short of breaking up her marriage, there is nothing that she can do about it. We've spent some hours on this, more than one visit. The final discussion with her ended like this: it seems that whatever you want or whatever I suggest, you are going to become pregnant and this means that the next baby also has a 1-in-2 risk of having Huntington's chorea. I said, "Now, you know that - put it out of your mind and remember that your baby has a 1-in-2 chance of being perfectly all right and try very hard, purely for your own peace of mind, to think in the positive sense." There was no other situation open to us. We had explored everything. I did what I possibly could to get her to look optimistically at what there was left in her life. The pregnancy is so far advanced that the question of terminating it doesn't arise. Many of my patients are Catholic or have other reasons for not even dreaming of terminating a pregnancy and, in fact, insist upon going on with it. And what I am trying to do, as far as possible, is to try and help them to cope with what is obviously a frightening situation. There is no way of gauging one's success in this, no matter how complicated a questionnaire I send out subsequently.

Let me just cite another instance because, perhaps, some here would give me advice on how to handle this situation.

Quite near to the Mayo Clinic there is a young couple. They are Catholic. The mother has rheumatoid arthritis. She is only twenty-three years old, so she has the unusual juvenile type of rheumatoid arthritis. Her first baby died of

interstitial pneumonitis, sometimes called the Hamman-Rich syndrome. The baby died during the first week of life. The second little girl is still alive but she has a great deal of respiratory problems. She is a bright, attractive little girl but she is regularly getting respiratory illnesses. Another baby has died and a third baby has died of the same interstitial pneumonitis - so we can call this the familial kind. They came to me and said. "What are we going to do?" They have had long discussions with their priest; they have been to see me and various other people half a dozen times, and I can only say there is clearly a high risk. I can't give them a figure because quite honestly I don't know the genetics of this particular syndrome. What I have simply said to them is: "Do me a personal favor. Try not to have another baby for another year and during this time I am going to ask everybody that I know if there is anything that we can do as far as the next baby is concerned. In other words, should we have a team standing by to handle the baby from the moment it is born? Should we put the baby into a high pressure oxygen chamber? Should we start the baby on steroid therapy or should we even give the mother steroids before the baby is born?" What I've done, in other words is to accept the inevitable and to bolster the morale of a nice young couple. This is not population genetics. It is a plain, common doctor-patient relationship, each patient being carefully assessed and handled on their own terms with a great deal of the genetic counsellor's and the patient's emotions coming into the discussion. I can't give you the statistics. I can't tell you what the chi-square results are going to be, but one does one's very best accepting that the results are inevitable. This is purely an ex-

tension of good medical practice. There is nothing peculiar to genetic counselling in this respect.

TRACY B. PERRY (McGill University, Montreal, Canada): Dr. Gordon, I don't see how these people can be expected to know what the alternatives are. How, for example, would they know about amniocentesis?

DR SHAPIRO: I think that it is fair to say that Dr. Gordon's views on genetic counselling are unusual. They certainly differ from mine. My anecdote is diametrically opposite to Dr. Gordon's. This concerns a young woman who had a mongoloid child. She was not told of the risk of recurrence, although this occurred at a time when amniocentesis and elective abortion were available. She became pregnant again shortly after the birth of her mongoloid child. She knew only what Down's syndrome meant and what it represented, became upset at the idea that she was pregnant, was not able to avail herself of genetic counselling, had a criminal abortion and died of complications of the abortion. This is obviously an extreme example, but genetic counselling would have provided her with an idea of the true risks. Had the small risk been unable to calm her, knowledge of the availability of amniocentesis might have saved her life and the life of her unborn child.

RONALD G. DAVIDSON (State University of New York, Buffalo, New York): Suppose we are consulted by a mother of a mongoloid child, who, let us say, is a translocation carrier, receives genetic counselling and then goes on to have a second mongoloid child. I think that this woman would have good grounds for suing the physician

on the basis of withholding information from her. I imagine she would have a pretty good case.

CHARLOTTE LAFER (Suffolk County Department of Health, Riverhead, Long Island, New York): I would like to make two points: one is that more babies have been saved by amniocentesis than have been aborted. Many of the patients who come for amniocentesis have fetuses that are shown not to be affected. The other is, in a relatively sophisticated community, the genetic counsellor will, in many times, be forced to do an amniocentesis to save the baby. One case in point: a woman had two sons. She was convinced that they had muscular dystrophy. They did not have muscular dystrophy but she felt that she had two affected sons and she had heard that this was an X-linked condition. She became pregnant and announced that unless the next child was a female she would have an abortion. Amniocentesis was done. She did have a female and this child was saved.

DR. CHASE: Had the child been a normal son, it would have been aborted - is that right?

DR. LAFER: Yes.

DR. HOOK: I wonder whether there might not be an alternative that would be acceptable to Dr. Gordon. Suppose a mother came to you very early in her pregnancy, who was a translocation carrier and had a significant risk of having a mongoloid child. Before even going into the question of amniocentesis, as long as you know that this is a situation that could be subject to that procedure why not just refer her to another genetic counsellor? Because of your own view, you are already essentially making a decision for her by not

saying anything, which may deny her the possibility of exercising her moral right to make a decision for herself.

DR. GORDON: I think it is a reasonable approach and I might take it. But this is a rare situation. I see patients for counselling every afternoon of the week. This means that I see several hundred patients over the year. Now, when the amniocentesis era began, I immediately realized there might be a conflict with my conscience . But it is remarkable that in two years I have had no trouble. I say this again to deemphasize the importance of amniocentesis in day to day unselected genetic counselling. I see the most remarkable range of patients and problems in relation to genetics and yet during the past two years, the question of amniocentesis has really only arisen on two occasions and I have been able to reject them straight away. One woman wanted to know if a curved little finger would be detected by amniocentesis. She knew it ran in the family and she didn't want that baby to be born with a curved little finger. Well, I dismissed her as courteously as I possibly could! The other situation arose in what you might regard as a rather important situation. A young woman with two miscarriages and a baby with Down's was pregnant again. In this situation, the baby had a standard G trisomy anomaly and both parents had normal chromosomes. The mother subsequently had a perfectly normal baby. Now, that patient was actually referred to an obstetrical colleague as a possible candidate for amniocentesis and I said to him, when he called me about the case, that if, in fact, the mother were a translocation carrier, I would arrange for them to see someone who would proceed with amniocentesis.

DR. HOOK: Let me get the second example straight. You had a situation in which the obstetrician had a couple who already had one mongoloid child - a young couple - and he wanted to consider amniocentesis because of the possibility of a recurrence and you made the decision not to do cell culture on the amniotic fluid which he would ordinarily have been willing to obtain. On what grounds?

DR. GORDON: Very simple. The fact that the baby had standard trisomy 21 Down's anomaly and that the mother and father both had normal karyotypes. I told the obstetrician that in my opinion the risk was one percent or less and he said that if that was the case he would agree that amniocentesis was not indicated.

DR. HOOK: What did you tell the parents?

DR. GORDON: Exactly the same thing.

DR. HOOK: But did you point out that the risk could be defined precisely with amniocentesis?

DR. GORDON: Whenever an authority speaks or writes about this, great emphasis is laid on the fact that this is an experimental tool and there are all sorts of questions about risks and dangers and hazards for which we do not yet have data. I'm not doing experimental work on amniocentesis. Perhaps, in the fullness of time, when I am presented with published statistics about risks and dangers and hazards, I may think differently. But, at the moment, I'm informed by the literature that this is an experimental procedure. I think that you might have been as horrified as I was to get a circular in the mail offering this as a service, saying in effect,

just send us some fluid and we'll tell you the results. Far from being concerned about the legal implications of not doing an amniocentesis, I wonder what the legal implications are when a complication does occur. What is going to be my moral situation when I'm asked by counsel to give evidence against someone who has done amniocentesis. Someone is bound to come to me and say we know you don't like amniocentesis, but a woman had an amniocentesis and was told that the baby was not going to have Down's anomaly but the baby had a cleft palate and we hear this could have been due to amniocentesis. I'm not really sure what attitude I'd have to take under those circumstances. So, you see, I've got my legal problems, too. The one legal problem I'm not scared of is anyone suing me for not destroying a life.

JERRY CARTER (Roger Williams General Hospital, Providence, Rhode Island): There is one thing I haven't heard throughout the whole session today and this is the role of the family physician in genetic counselling. In many cases, the family physician can play an important role in helping a family decide exactly what will be done in case of a pregnancy where there is a genetic risk and I think it is incumbent upon the medical geneticists to make a greater effort to train family physicians along these lines.

DR. GORDON: I would entirely support your contention about the general practitioner. The greatest satisfaction I've had in genetic counselling is the close rapport I've been able to establish with a great many general practitioners in my area. Practically all the patients I see for genetic counselling are referred to me by general practitioners. I'm not the primary

physician and all I do is discuss, to the best of my ability, the genetic aspects of the problem and then communicate, if possible, personally and certainly by letter to the people who have come for genetic consultation. I have had a great deal of personal satisfaction out of the positive aspects of genetic counselling. The last thing I always say to parents is that if they have another baby, please write and tell me about it and, so far, the results to date have been highly satisfactory. Most parents, I think, have been given a good genetic prognosis and have decided to have children and the results have been very satisfactory to me - and the parents. I am not in the least bit concerned about the fact that I do not have amniocentesis available.

THE IMPACT OF MAJOR MALFORMATIONS ON SOCIETY: ENVIRONMENTAL VERSUS GENETIC FACTORS

Dwight T. Janerich

Congenital malformations have a dual effect on society. The primary effect can be seen in the physical resources which we use to deal with the social and health problems which they create. In addition, a large emotional cost is also part of the primary effect of the occurrence of congenital malformations. The secondary effect is less evident but may be more important, particularly if the cause of these malformations is found to be predominantly genetic. Their occurrence would then imply that man's genetic framework is quite fragile, and the development of adequate preventive measures would be expected to be relatively difficult.

A measure of primary effect of congenital disease can be obtained from an examination of data on congenital malformations and stillbirths from upstate New York.[1] The term congenital disease is used here in the broadest sense and includes biologically destructive processes superimposed on normally developing tissues as well as abnormal tissue differentiation and development.[2] During the last ten years, about two percent of all births were stillborn- the cause of death was frequently an obvious congenital malformation. Another one percent were born alive with a major congenital malformation which was diagnosed at the time of

birth. About thirty percent of these children died before they were one month old. The remainder will live long enough to require treatment or be institutionalized as a result of impairment from their defect. When we add to these the large number of early spontaneous abortions and the large number of less obvious congenital malformations which are not diagnosed until some time after birth, it becomes clear that man's reproductive mechanism is not efficient. By all estimates the costs incurred by this inefficiency are immense and the results of the best corrective measures are often far from satisfactory.

At the present time, over five percent of all births are affected by some type of congenital defect. In the first half of this century the rate was even higher. The stillbirth rate in 1925 was 39 per 1,000 births; in 1965 the rate was 19 per 1,000 births. The stillbirth rate and probably the congenital malformation rate declined through 1950 but has stubbornly resisted improvement since. To further reduce the rate of congenital disease we are employing the tools provided by genetics, embryology and epidemiology.

The direct impact of congenital disease is severe, but its implication on the quality of man's make-up may be even more important. The relatively frequent occurrence of congenitally defective births poses the question, "Is man still at a relatively primitive stage of evolution, intensely sorting out his genetic background through selective survival - or is his genetic make-up relatively stable but he is unable to cope with the new environmental conditions which he is encountering through his efforts to organize his society?" The answer to this question is likely to fundamentally

affect the future of human society.

The importance of this question is best seen from the perspective of our very limited knowledge of the etiology of congenital disease. We understand the cause of less than twenty percent of all congenital disease and by most standards this would be a liberal estimate. Where we have discovered the cause, we can develop and apply preventive measures. If the disease is genetic in origin, and its occurrence is inherited according to a recognized pattern, genetic counselling is the preventive measure. If the disease is caused by environmental factors such as rubella or thalidomide, different approaches are used. We employ population surveillance to help us recognize unusual clusters of malformations and eliminate the cause. Laboratory testing can screen new compounds before they are recommended for human use thus avoiding human consumption of teratogenic agents. In the case of rubella, measures such as the vaccine can be used to lessen the possibility of exposure of pregnant women to the teratogenic agent.

However, if we were to apply all available preventive measures with maximum efficacy, we would still be unable to affect the occurrence of the majority of congenital disease. The reason for this deficiency is clear - we do not yet understand the cause of most congenital disease - or more specifically, we do not know enough about their cause to develop adequate preventive measures. Research is needed to rectify this deficiency. Yet, the amount of resources which can be directed to these research problems is small and progress is slow. But, progress is necessary if we are to lessen the damaging effect which congenital malformations have on human society. We must find ways to ascertain

whether the occurrence of congenital malformations is determined primarily by genetic factors or whether they are primarily the result of environmental factors. The information is essential, not only to determine the direction which we should take in our research efforts but to help in building the type of society which will assure the development of man's full genetic potential.

In many common congenital diseases neither abnormal chromosomes nor mutant genes can explain their occurrence. Yet, family studies suggest a genetic predisposition. In these cases, the concept of polygenic inheritance has been proposed to explain the causal mechanism. In the broadest sense this concept suggests that the cause of many congenital malformations can be found in the interaction of a number of genes or gene-products and perhaps environmental factors. If this concept is correct, and the dominant factor is genetic, it implies that man's hereditary make-up contains a large number of genetic liabilities and we would have little hope for the development of effective preventive measures in the near future. If, on the other hand, the predominant factors are environmental, we could be optimistic for the development of adequate preventive measures. Not only would these preventive measures have the effect of reducing the incidence of congenital malformations, but it would probably improve the health of all individuals by assuring optimal environmental conditions during the critical period of prenatal development.

Thus far, epidemiologic studies have been unable to identify environmental factors which explain more than a small portion of human congenital malformations. This has led many to conclude that the explanation lies in genetic

factors, or that the causative environmental factors are not yet recognizable with available technology. Another possibility is that the cause is environmental but in some way acts before the affected pregnancy. However, this possibility is difficult to investigate from an epidemiologic point of view. A cohort approach is necessary. However, retrospective data precludes a definitive study and the development of prospective cohort data would require large expenditure of time and money.

Polygenic inheritance has been suggested as the causal mechanism in anencephalus, spina bifida, cleft lip and palate, club foot and several other common congenital malformations.[3,4] Recently, anencephalus and spina bifida have received renewed research attention. One reason for this renewed interest is that these malformations show great variability in incidence over time. This secular variability is often severe enough to label periods of peak incidence as epidemics. These apparent epidemics, together with changing family recurrence risks and the variable risk associated with birth order and season of birth, strongly suggest that environmental factors affect the incidence of these malformations. Yet, time-space cluster analysis of conditions present during affected pregnancies fail to clearly identify relevant environmental factors.

The most dramatic epidemic of anencephalus and spina bifida ever described occurred in the northeastern United States from 1920 to 1950.[5] It reached its peak in the early 1930's. No epidemic of congenital malformations of this magnitude has ever before been recorded. It dwarfs the thalidomide and all rubella epidemics by several orders of magnitude. Its recent description by Doctors MacMahon and Yen probably represents a milestone in the epidemiology of

congenital malformations. It was probably not recognized as an epidemic at the time of its occurrence because these malformations were not systematically recorded and attitudes about congenital disease were considerably different at that time.

The dramatic nature of the epidemic strongly suggests that it was caused by environmental factors. Although the period of increased incidence is over, investigation of it holds the promise of new and valuable insights into the causes of congenital malformations.

Several hypotheses have been suggested to explain this epidemic. All involve environmental factors. One possibility is that it was related to the consumption of a contaminant of illicit alcohol during the period of prohibition from 1920 to 1933. However, this does not exactly explain either the peak or end of this epidemic, particularly since a secondary peak was seen in the early 1940's.[6] A second possible explanation involves the observed relationship between socio-economic status and the incidence of these neurological malformations. Since the rate of these defects is higher in the lower socio-economic strata, it has been theorized that the effects of the great depression may have caused the epidemic. Again, there are discrepancies in time which must be accounted for if this explanation is to be invoked. A third possibility involves a cohort mechanism whereby the epidemic may be explained by the reproductive activity of a cohort of women who were born between 1905 and 1910. The peak of the epidemic and the peak reproductive rate of these women coincide. Preliminary studies suggest that the epidemic may have been caused by a series of high risk cohorts with the most severely affected being those born between 1905-1910. It will probably

not be possible to determine the cause of the high risk of nural-tube defects which may have affected the offspring of these women, with absolute certainty from retrospective data. One possibility is the particular effect that those women suffered from the great influenza[7] pandemic of 1918. Evidence that these women were particularly affected can be seen in the age and sex-specific deaths from influenza during the height of the epidemic. Although the time elements fit well, a biological explanation is lacking. It is possible that the severe illness which accompanied this epidemic, in some way interfered with the maturing reproductive mechanisms of these females. If a cohort mechanism is proven, we may then find an enciron-mental explanation for family clustering which has in the past invoked an explanation based on genetic factors.

A great deal of research remains to be done before any of these hypotheses can be rejected or confirmed but this research offers a great hope for understanding the environmental causes of congenital malformations and thereby devel-oping effective preventive programs.

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SECTION V

SOME COMMENTS ON THE SIGNIFICANCE OF SEX CHROMOSOME ABNORMALITIES IN HUMAN MALES

Ernest B. Hook

INTRODUCTION

An unexpected discovery in recent years has been the apparent association of sex chromosome abnormalities in the human male with antisocial deviant behavior. Prior to this there was nothing in our knowledge of cytogenetics or behavioral genetics of lower organisms that would have led us to predict such an association in man.

It is also striking that two separate male genotypes, XYY and XXY, have been correlated with deviant behavior but no sex aneuploid state associated with a female phenotype has been so implicated. It should be emphasized, however, that both the XXY and XYY genotype has occurred in many individuals with "normal" behavior so that a chromosome finding of this type will not predict future development with the same confidence, for instance, that trisomy 21 will predict mental retardation.

The optimal method to document an association with antisocial behavior would be to follow XYY or XYY individuals from birth. It is likely that by the end of the decade or so, this approach will be productive. At present, however, our conclusions are based upon determination of the rates of XYY and XXY individuals in various

settings for antisocial behavior and comparison with the rates in background or normal populations.

XYY GENOTYPE

There are sufficient data already in the literature to suggest that the incidence rate of XYYs is about 1/700 births or about 0.14% at least in the white newborn populations of Great Britain and North America.[1,2,3,4,5] Two small studies in North America have found rates of 1/250 or 0.4%,[2,3] but the 95% confidence limits of all studies overlap a rate of about 1/1000 or 0.1%. It is certainly possible that there is heterogeneity in the background rate even within relatively homogeneous populations, so we will consider two background newborn rates for white XYYs, one a maximum conservative background rate of 1/250 or 0.4% and the other the currently available mean background rate of 0.14% or 1/700. (We have no data at present derived from large numbers of non-white newborn males.)

The available data from institutions concern adult populations born some years earlier and there are no data on the newborn rates at earlier times. What is known of contemporary "normal" adult populations suggests that the use of contemporary newborn rates for comparison will at least not underestimate the number of XYYs in the total adult population, so this also represents a conservative approach.

A number of institutions in which deviant individuals may be found have been studied. These can be distinguished by the stated criteria for admission or inclusion as "mental", "penal" or "mental-penal". Mental settings are those for the retarded or mentally disordered; penal settings are simple security settings such as

general prisons, whereas mental-penal settings meet both criteria.

The first study to suggest an association of deviance and XYY genotype was carried out in a mental-penal setting by Jacobs et al. in 1965,[6] and reported a rate of approximately 3% XYYs, a marked increase over the subsequently determined newborn rates.

Eleven comparable reports of mental-penal settings of which I am aware (in which at least 20 individuals have been studied) had appeared as of September 1, 1971. Of these eleven, in 10 the observed rate of XYYs was greater than the presumptive maximum newborn rate of 4%, and in one it was lower. (There is also one unpublished study known to me, in which the rate was lower.) Eleven other studies of mental-penal settings (in which there are over 20 inmates) have been done restricted to tall inmates. (The original report of Jacobs et al. indicated that XYYs are, on the average, taller than XYs. Many workers in attempts to ascertain XYYs have thus restricted studies to tall individuals only. The number of detected XYYs divided by the total size of the institution (if known) thus yields a minimum rate of XYYs in this setting, and if this is greater than the background rate there is clearly an enrichment of XYYs in the entire setting. On the other hand, if the rate of XYYs in <u>those tall inmates studied</u> is less than the background there is no enrichment of XYYs in the entire setting. Otherwise no decision is possible.) In five there was an increase of XYYs, in four no decision was possible and in two there was no increase. Thus, of a total of 23 published studies (including the original one) in 16 there were definitely more XYYs than background, in four no decision was possible and in three there was no enrichment. Of the latter, two were of rela-

tively small numbers and the absence of XYYs is not significant in a negative sense. The third was of 60 tall retarded prisoners and this remains to my knowledge the only contrary published negative report.[7] (The already cited unpublished negative study (not height restricted) was of a large number of acutely disturbed prisoners in a major city referred for psychiatric examination at a county hospital. Possibly the fact that this was an evaluation setting and not a final placement may be significant here.)

If we take the available rates for the 13 mental-penal settings for which complete data are available, we find that the average rate of XYYs is 2.0%. This rate is five times the maximum presumptive newborn rate of 0.4% and 15 times the probable newborn rate of 0.14%.

In 27 exclusively penal groups studied of over 20 individuals, seven have yielded rates equal to or greater than the maximum presumptive background rate while six have yielded rates below this. In those which are "positive" and for which exact data are available, the rates are all lower than the average of 2.0% found in mental-penal settings.

Similarly, study of exclusive mental settings has revealed no consistent increase in the number of XYY individuals (except in security wings of such units which have been classified here as mental-penal settings).

Reports from exclusively mental or penal settings may have led some to suggest prematurely that the initial suggestion of an association or deviance with the genotype was in error[8] but while the extent of the association may not be as some suspected initially, it is clear that there is an increased risk for an XYY to eventually appear in a mental-penal setting.

It is more difficult, however, to decide <u>why</u>

XYYs have this increased risk. While some greater trend to some type of brain dysfunction leading to behavioral abnormality may be responsible, there is no direct evidence for this in many cases. The explanation must remain speculative at present. It seems at least likely that large height per se is not responsible.[9]

Another question is whether whatever causes the increase in deviant behavior has a "threshold" for manifestation. For instance, if some type of cryptic neural dysfunction were responsible for the entire increase of deviance, only the presumably small proportion of XYYs in custody might be affected. But if the (presumed) responsible physiological factors have a "continuous" effect upon behavior then there may be a very high rate of XYYs whose behavior is deviant but not as markedly so as those in custody. The absence of a marked increase of XYYs in exclusively mental or penal settings seems more consistent with the threshold hypothesis, but clearly further work is necessary here.

THE XXY GENOTYPE

The phenotype associated with the XXY chromosome constitution, the so called Klinefelter's syndrome, has been known far longer than the human XYY genotype. It is only relatively recently however, and partially as a consequence of discovery of the latter that the extent of the association of deviance and the XXY genotype has been recognized.

The evidence derives at least in part from study of populations already described. More data are available on the incidence of XXY in the "normal"newborn population and it seems likely that 0.2% or 1/500 can be taken as a reasonable presumptive upper bound on the rate, although

here too there may well be heterogeneity between groups. Of the 12 published mental-penal settings which were previously cited, in 9 the rates of XXY were greater than this figure and in 3 lower. The mean rate was 1.3% (lower than the mean rate of 2.0% XYYs in these institutions) or about seven times the background rate of 0.2%. Thus, the rate of XXYs while greater than the background rate is not as markedly increased as that of XYYs in the same settings. (We cannot use data derived from the much larger number of sex chromatin surveys unless the chromatin positive males have been karyotypes, since both XXYs and XXYYs will be chromatin positive.)

There is similarly, no consistent increase of XXYs in simple penal settings. Evidence from sex chromosome studies which have been supplemented by chromosome studies indicate however, that XXYs are consistently increased in at least some mental settings; those for the high grade mentally retarded.

With the proviso that there seems likely to be a greater frequency of retardation but a lesser increase of deviance in XXYs, the same discussion already presented concerning the origin or anti-social behavior in XYYs can be invoked here. (Since the XXY male unlike the XYY male is hypogonadal, one possible exception is that changes in body image from early adolescence on might thus be responsible. There is no evidence that hypogonadism in XYs is associated with deviance, however, whereas comparison of hypo-gonadal XY and hypogonadal XXY males indicates that the latter generally have had greater difficulty in social adjustments.[10,11])

THE XXYY GENOTYPE

The newborn incidence of this genotype is

probably of the order of magnitude of 0.01% (1/10,000) or less. As might be expected, judging from the population studies already cited XXYY individuals also have an increased frequency of deviance (as well as mental retardation). There is not enough data yet gathered to indicate how much greater the prevalence of antisocial behavior is in these individuals compared to XXYs or XYYs.

CONCLUSIONS

While the number of XXYs and XYYs in the population is very small and the number of markedly deviant such individuals probably much smaller, the importance of these syndromes cannot be dismissed. Any two disorders which alone account for almost one in thirty inmates of mental-penal settings are worth further study, if only for that reason. But it is clear that with the population studies and anecdotal case reports accumulated to date, we are only at the end of the beginning of our knowledge concerning these conditions.[12]

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DISCUSSION

DR. BANNERMAN: In cases of XXY or XYY ascertained at birth, what would you advocate telling the parents.

DR. HOOK: My own inclination would be not to tell the parents initially, to avoid sensitizing them to the possibility of something that, after all, might not develop. I believe the child should be closely followed medically, however, and if the family moves, the new physician should be informed as well. If antisocial patterns do emerge, it may then be worthwhile to inform the parents that there is a genetic hypothesis to account for this development. This may relieve them of guilt feelings concerning their role as parents. In addition, should some possible therapy emerge in the future, it will be important to have kept track of patients whc might benefit therefrom.

LAWRENCE SHAPIRO (Letchworth Village, Theills, New York): I think one of the problems is that when you have an individual with XYY who is normal, or sublimating whatever problems XYY involves, stigmatizing him with the designation XYY may be harmful and serve no useful purpose. For example, many people have tried to study football and basketball players and some clubs, when approached, realizing they might lose players, were unwilling to have their players studied.

In surveys of newborns, a small number of XYYs have been detected and, whether you tell the parents or not, if they are to be studied they have to be followed and one's concern is how to protect the individual's rights. How does one avoid stigmatizing such an individual, who is perfectly normal and may lead a useful life, and

yet continually follow his development to prove this point? Who keeps the records? How do you keep it out of the hands of those agencies, for example, who might use it against the individual? Despite the fact that we live in a democracy, with a certain degree of liberty and freedom, it is conceivable that this bit of information could be used to the individual's disadvantage.

DR. HOOK: This is a potential problem with almost any medical disorder and any type of record, medical or otherwise. I am struck, however, by the fact that government agencies in this country protect records such as census data and income tax returns with great conscientiousness.

ELLYN STECKER (Toronto General Hospital, Toronto, Canada): With respect to the XXY, not every patient with Klinefelter's syndrome will exhibit deliquent behavior, but every patient with Klinefelter's syndrome has the problem of his reproductive capacity. Is there anything one can do about this if the diagnosis is made at an early age?

DR. HOOK: The infertility is not likely to be correctable now or in the immediate future. Some patients have been given testosterone which may produce a better psychological adjustment. On the other hand, some patients who have received testosterone have become aggressive.

ELLYN STECKER: At medical rounds, in Toronto, there was a patient with Klinefelter's syndrome who was approximately 40 years old and was explaining his reaction to being given testosterone. He had been quite happy before but now he had acquired a whole set of new feelings which

he was not entirely sure how to handle. Perhaps, if we identify these patients at birth and start treatment earlier, we could prevent this effect from occurring.

THE SIGNIFICANCE OF SCREENING FOR INBORN ERRORS OF METABOLISM

Harold M. Nitowsky

INTRODUCTION

With increasing attention being given to the study of human genetic disorders, and the insights into intermediary metabolism that have come from recent advances in biochemistry, a great deal of medical and public health interest has been focused on the possibility of early and presymptomatic detection of patients with inborn errors of metabolism by laboratory tests. However, considerable controversy exists over whether or not mass screening programs are justified on the basis of present knowledge.[1]

Despite the arguments for or against mass screening, there can be no question that, once a family with an inherited disorder is identified by the birth of an affected child, every infant subsequently born into that family should be carefully studied, to permit as early diagnosis as possible. Similarly, there seems to be adequate justification for screening selected population groups in which the incidence of certain genetic disorders is sufficiently high to warrant detection of families at risk.[2] In these instances, prevention may be preferable to other less desirable alternatives, particularly when therapy for the disorder is ineffective and

severe incapacitating disease or death is likely. Prevention can be achieved by identification of heterozygous carriers of a recessive mutant gene, which provides a basis for premarital counselling as well as an indication for amniocentesis in early pregnancy when both parents are carriers and the disorder in question falls into the increasing number of recessively inherited inborn errors of metabolism that can be detected prenatally.[3] Of course, moral, religious or ethical issues arise when prevention by therapeutic abortion becomes a consideration for those disorders where treatment is ineffective and cure unlikely.[4]

The purpose of this paper is to review some general principles which apply to mass screening programs in general and particularly for inborn errors of metabolism and to evaluate the experience with selected programs of this type, pointing out some of their more controversial aspects. Brief reference will be made to some of the newer techniques for the detection of inherited metabolic disorders. Finally, potential areas for screening will be discussed in light of some of the recent developments in our knowledge of human biochemical disease.

1. The Target of Screening Tests for Inborn Metabolic Errors.

Screening tests for human inborn errors of metabolism can be classified in terms of the phenotypic level at which the consequence of the genetic mutation can be identified (Table 1).

a. Level of the Gene Product. Mutation can alter the structure or amount of a gene product (e.g. an enzyme or other protein) and this will be reflected in a change in the activity of function of the gene product in a screening test. On the other hand, screening methods may involve

detection of a qualitative change in the properties of the gene product (e.g. electrophoretic mobility or thermal stability). Screening at the level of the gene product often requires sampling of tissue, such as biopsy of skin or one of the internal organs. Although this approach may be very useful in the investigation of a single patient, it obviously is not compatible with mass screening. However, if the formed elements of blood or serum can serve as a source of the enzyme or protein, it may be possible to utilize this approach for purposes of mass screening. In recent years, increased efforts have been made to develop methods for direct assessment of enzyme activities in erythrocytes, leukocytes or plasma for purposes of mass screening.[5]

b. Level of Metabolic Intermediates. When the gene product, such as an enzyme, is involved in a metabolic pathway, alteration in enzyme activity will change the concentrations of the metabolic reactants. Detectable biochemical imbalance may then occur, either in the form of accumulation of the substrate of the reaction or as a deficiency of the expected reaction product. These events may, in turn, lead to further biochemical imbalance which can also be detected. Measurements of metabolites or nutrients in body fluids can then serve as the basis for a screening method.

A screening technique directed at this target level must be capable of detecting significant changes in the amount of the relevant chemical substance. Much effort has been expended in recent years to develop automated techniques with sufficient sensitivity and specificity for this purpose.[6]

Since factors unrelated to metabolism of a substance can lead to alterations in its concentration in urine or other body fluids (e.g.

renal function in the case of a urinary component) consideration must be given to alternative explanations for abnormal concentrations of metabolites in physiological fluids.

Biochemical imbalance detected by screening tests may not always be related directly to the primary enzyme abnormality of the mutant phenotype. The biochemical derangement could, in fact, be several steps removed from the primary genetic abnormality. For example, hypervalinemia may reflect impaired valine transamination in one type of inborn error,[7] but it may also reflect impaired decarboxylation at a later step in the catabolism of this amino acid, as occurs in maple syrup urine disease.[8] Other examples of this type of ambiguity are listed in Table 2.

c. Level of the Clinical Phenotype. The clinical disease which can result from an inherited or acquired metabolic impairment represents the most peripheral manifestation of the biochemical abnormality. Since a major objective of any mass screening program is to prevent disease, detection of patients at risk by their clinical disturbances is an indication of failure to fulfill one of the primary goals of the screening program.

2. General Principles in Screening for Inherited Metabolic Disorders.

There are several general principles which are applicable in considering any screening program for an inherited metabolic disorder:

a) the screening test must be effective, simple and easy to perform on small readily collected test samples which must be stable during shipment to the laboratory.

b) the screening test must be oversensitive, so that it identifies all the cases. Although false positive tests are acceptable, within

certain defined limits, there should be no false negative tests.

c) means must be at hand for the prompt study of all suspected cases by qualified personnel, using more accurate methods that will reliably identify the true cases or distinguish between genetic variants of a particular syndrome.

d) there should be an effective method of treatment for the disorder once it has been identified or one that offers some benefit to the patient.

Other principles can be listed but these are dependent to a large extent on the purpose of any screening procedure. A screening test may have one of three aims and the requirement for its acceptance and use may be quite different in each case. Firstly, screening may be used for purposes of research and the ethical issues are essentially similar to those which arise in other types of medical investigation. An example of research use is the validation of a screening program - it would not be possible to test for general application if it were not permissible first to explore its usefulness in smaller populations. When used in this way, screening cannot be expected to meet as vigorously some of the biological criteria referred to previously or the economic criteria to be discussed later.

A second and well established use of screening is for protection of public health. Although this aspect does not appear to be relevant in screening for inborn errors of metabolism, in the area of infectious diseases it has long been considered appropriate or even mandatory to identify a source of infection that might represent a serious public health threat. Here again, the aim of screening is such that it is difficult to impose the exacting requirements concerning efficiency and cost of the screening

test.

It is a third type of screening with which we are concerned - that is investigation which has as its primary aim neither research nor the protection of public health, but a direct contribution to the health of individuals. This has been referred to as "prescriptive screening" by McKeown and others.[9] It is to this last type of screening that a validation procedure should be applied before a test is regarded as useful and suitable for testing of mass populations. To achieve this aim, the validation procedure must be comprehensive; it should include economic as well as biological assessment and requires evaluation in relation to alternative methods of diagnosis as well as efficacy of therapy.

3. Procedure for Validation of Screening Tests.

a. Definition of the Problem. Screening programs should not suffer from vagueness or confusion of aims. At the outset it is essential to define the problem under investigation, its medical significance, the groups to be screened, the stage of detection, the tests to be applied and the methods required for confirmation of the diagnosis. Equally important are questions related to therapy and the requirements for follow-up care in terms of personnel, laboratory resource and other aspects of therapy.

b. Knowledge of the Disorder. A significant aspect of any prescriptive screening program is knowledge of the variability and natural history of the disorder in question. For many reasons, the problem of unravelling the natural history of disease is a formidable one and often requires observations of large populations for prolonged periods.

c. Adequacy of the Screening Procedure. The

proposed screening procedure must be examined critically. This requires first an appraisal of the diagnostic test, its sensitivity and specificity, its feasibility, etc. It should be borne in mind that screening for inborn metabolic errors can ascertain disease only at an approximate level. No test can be expected to assure complete identification of a disease or trait.

The frequency of occurrence of false negative results will depend partly on the nature of the test and partly on the biological variability of the disorder in question. A test of enzyme activity, for instance, may discriminate clearly between normal activity and greatly reduced or absent activity. If all patients with a particular disease had no activity of the enzyme in question, then all patients, at least in theory, should be identified by a test which screened directly for enzyme activity.

On the other hand, if the screening test is based on measurement of substrate accumulation in response to altered enzyme activity it is possible that screening for the disorder would be less sensitive. Substrate levels may be affected by nutrition or dietary exposure, by the activity of alternative metabolic pathways, by renal function if it is excreted in the urine, and possibly other factors. Testing for abnormal or diminished amounts of normal reaction products may be fraught with even greater difficulties since the occurrence of enzymes in alternative catabolic pathways can vary and, as a result, so can the level of secondary reaction products (e.g. urinary phenylpyruvic acid in phenylketonuria).[10]

The frequency of false negative tests is also a function of the technical sensitivity of the test. In the case of any parameter that has a continuous variation in the normal population,

a test with a high cut off point for discriminating between the normal and abnormal phenotypes may accurately identify affected persons, but also will include many false positives.[11]

Relatively little is known at present about the effect of normal biological variation upon the frequency of false negative or positive tests in mass screening programs for many of the inborn errors of metabolism involving the amino acids or other substituents. It has been stated that in the Massachusetts program for detection of phenylketonuria, 5 percent of patients with this disorder escape detection on the first test for hyperphenylalaninemia, which is performed shortly after birth.[12] In this instance, the sensitivity of the test for phenylalanine blood levels can be arbitrarily predetermined within broad limits.[13] However, the biological variation in postnatal expression of hyperphenylalaninemia is related to variations in type and duration of diet, time of testing as well as other factors, and these apparently account for the false negative results.

False positive tests present another difficulty in the interpretation of screening tests. In such instances, a positive test does not indicate the presence of the disease in question. In some cases this may reflect a technical artifact. However, interpretation is more difficult if the positive test reflects a form of biological variation other than that due to disease. Inherently, false positive tests are acceptable or even desirable if they eliminate or minimize the possibility of false negatives provided, of course, that adequate resources are available for confirmation of the diagnosis in the suspected cases prior to the institution of any therapy or permanently labeling the patient as "affected". An unfavorable outcome of therapy because of

inappropriate treatment in circumstances where there was inadequate understanding of the variable expression of a disorder or validation of the diagnosis has accounted, in part, for some of the adverse reactions to screening programs.[1] Thus, individuals with positive tests must be properly evaluated to avoid misinterpretation of test results. Often, these studies have elucidated new forms of normal biological variation of heterogeneity in a disease entity.[14]

d. Adequacy of Therapy. The same type of scrutiny that is applied to the test procedure should be applied to the proposed treatment program. Is it effective? If alternative approaches to therapy are available, which one is the best? How can therapy be accomplished most efficiently? What are the expectations in regard to compliance with the recommended treatment regimen? What type of follow-up is necessary and what are the mechanisms available for continuous monitoring of the patient if the treatment imposed makes this mandatory.

Whenever evaluation leads to the conclusion that a screening procedure is not validated in regard to all these considerations, and this is often the case, proposals are needed for the acquisition of the requisite additional evidence. In some conditions considered for screening, the deficiencies of knowledge are so great that it is inconceivable that they could be met by a single inquiry. In such instances, it is nevertheless of value to clarify the issues and to show the extent of the information needed before screening on a mass basis can be seriously contemplated.

When a screening procedure has been validated, it is still necessary to consider carefully the way in which it is to be applied. Such decisions may be simple or extremely difficult. For example, it may be necessary to decide whether on

grounds of usefulness or risk, etc., a procedure should be directed at a selected population group and, if it should, how to ensure that the program reaches or is limited to those for whom it is intended. In practice, this aim may be difficult to achieve, for it may not be those at greatest risk who present themselves most willingly for investigation. Account must be taken of these and other difficulties in the initial design and subsequent application of extension of screening programs.

In summary then, before the issue of the biological soundness of any screening procedure can be resolved, we need to know a good deal about the natural history of the abnormality, to be able to identify it at an early stage by screening and to have methods of treatment or intervention which will benefit those affected. Unfortunately, at this juncture, apart from a few conditions, such as phenylketonuria, there are not many inborn metabolic errors in which these requirements are met.

3. Questions of Priorities and Cost.

In addition to the principles which relate to the effectiveness of a screening procedure, consideration has to be given to the question of priorities - does a mass screening program make better use of limited resources than the available alternatives? Thus, the criteria for screening programs are both biological and economic.

The economic considerations involved in mass screening programs derive fundamentally from medical measures, but they are particularly significant in the case of screening programs because of the scale on which they are applied. Although screening can be applied to selected individuals, or to small population groups, and

indeed, may have ample justification on this basis, it is essentially a procedure for application to large populations. There are several reasons for this. In the first place, the detection of presymptomatic disease presupposes investigation of groups in which a majority, and usually a large majority of those examined, are not affected. Secondly, the justification for screening is, in part, that it is economical, and the economies depend to a considerable extent on large scale methods of collecting, analyzing and interpreting data. Thirdly, once a screening program has met the stringent biological and economic criteria which should be applied, its benefits should be shared by as many individuals as possible.

However, although the benefits which may result from extensive screening are large so, too, are the associated risks. A procedure widely applied without adequate biological or economic assessment may consume vast resources before it is discovered to be ineffective or inefficient. It should also be recognized that since public finance is limited, and this is true even in the most affluent societies, medical measures compete with one another as well as with a variety of social services. The introduction of an elaborate and costly screening program is often done at the expense of other medical use of the same resources and should be accepted only when it is more rewarding than the measures displaced. For obvious reasons, therefore, acceptance of any screening program for general use should be preceded by a stringent validation procedure, in which economic as well as biological criteria are examined critically and comprehensively.

4. Experiences with Prescriptive Screening for Phenylketonuria.

Phenylketonuria (PKU) has been widely assumed to meet all the requirements of prescriptive screening. This is a disorder which apparently results, if untreated, in lasting physical or mental handicap; the screening methods developed can detect the abnormality, if present; treatment can be given to those affected; and the pre-symptomatic screening approach appears to make efficient use of available resources.

Let us examine these contentions critically and, in the desire to be objective, we shall review them in historical perspective. I believe that we shall be forced to the conclusion that our knowledge of the natural history and variability of PKU is incomplete, that the effectiveness of treatment of the disease has not been accurately measured, that we have adequate information about the optimal age for institution of therapy, or the levels of serum phenylalanine (PA) at which treatment should be undertaken, or the age at which treatment should be undertaken or the age at which treatment may be stopped. Despite all these unanswered questions and the obvious lack of adequate validation of prescriptive screening for PKU, I do not believe we can, or should, turn backwards. Our intuition and empirical judgements, stemming from the accumulated evidence, inadequate though it may be, would deter us from altering current practice with regard to PKU. However, the lessons we have learned from our experiences with this disorder should serve as a warning against any impulsive or premature extension of prescriptive screening to a variety of other inborn errors of metabolism which are associated with serious illness or mental subnormality and for which screening tests are available as well as the possibility of dietary control.

The concept of PKU as an inborn error of

metabolism remained relatively static from the initial observations of Folling, who in 1934 demonstrated the presence of phenylpyruvic acid (PPA) in the urine of these patients and elevations in their serum PA levels,[15] until the early 1960's. Folling's findings were substantiated by Jervis, whose studies suggested a greatly reduced activity of the enzyme which converts PA to tyrosine.[16] Armstrong and his colleagues showed that often a considerable time after birth had to elapse before PPA could be detected in the urine of newborn infants with PKU and that its detection was unlikely if the serum level was less than 15 mg. per 100 ml.[17] Obviously, infants screened for the disease at too early an age, or those with only minor elevations in serum PA, would be missed by urinary screening.

Since early screening programs for PKU were based upon ferric chloride testing for PPA in urine, conceptually, PPA was linked with the increased serum PA in one direction and mental retardation in another. The notion that increased serum PA inevitably results in mental retardation was perpetuated as long as urine testing was the sole method for mass screening. However, even early investigators were aware that elevated serum PA was not always associated with retardation and older "atypical" or intellectually normal children who manifested the biochemical abnormalities of PKU were detected when families were screened after identification of a PKU infant.[18]

A strong incentive for prescriptive screening of newborn infants stemmed from the report by Bickel and his colleagues in 1953 that PA restriction was associated with improved development and behavioral performance in a PKU child.[19] They suggested that retardation might be pre-

vented if dietary treatment was started in infancy. This report also provided an impetus for the development of a more reliable screening procedure than the ferric chloride test for PPA, one that, at the very least, could detect cases at an earlier age.

The introduction by Guthrie and Susi in 1963 of a relatively simple and sensitive mass screening method for elevation of serum PA[13] has resulted in a remarkable revision in our concepts about PKU. The discovery of hyperphenylalaninemic conditions, which to a variable degree biochemically can mimic classical PKU, has demanded increased knowledge of the pathophysiologic features of PKU and its variants and has necessitated a change in our attitudes toward diagnosis and management.

The Guthrie screening test was rapidly and widely adopted for the early detection of PKU in newborn infants and, indeed, the test has become mandatory by law in a majority of states in this country and in other countries as well.

One of the first unexpected consequences of prescriptive screening for PKU was that many more infants were identified with elevated serum PA levels than would have been predicted on the basis of previous survey data from populations of mentally subnormal patients. It was difficult to reconcile these differences at the time. The birth incidence of PKU before 1963, based on data from retarded populations, was estimated by Knox to be between 1:20,000 and 1:25,000 among individuals with mixed European ancestry.[18] On the other hand, results of mass screening of newborns in Massachusetts by the Guthrie method gave an incidence of approximately 1:14,000.[12] The latter figure did not include patients with hyperphenylalaninemia associated with transient tyrosinemia, which has been shown to be the most

frequent cause of transient mild elevations in serum PA in newborn infants.[20]

With further screening it became evident that some hyperphenylalaninemic infants and children without concomitant retardation accounted for a portion of the discrepancy,[21] and the discovery of these variants caused a minor upheaval in our concepts about PKU. A similar sequence of events has occurred with metabolic disorders involving other amino acids. Biochemical abnormalities in homocystinuria, cystathioninuria and histidinemia were first detected in patients who were retarded or appeared retarded; more extensive screening has revealed that persons with obviously normal intelligence possess the same biochemical aberrations.[22]

With time, increasing numbers of hyperphenylalaninemic but clinically normal infants and children are being recognized who have intermittently positive ferric chloride tests and variably increased excretions of the characteristic urinary metabolites of PKU: PPA and orthohydroxyphenylacetic acid (O-HPAA). These variant patients, who at times biochemically simulate PKU patients, are an enigma and the cause of great confusion. Variants have made the definition of PKU arbitrary to clinicians and other investigators. Guidelines for the treatment of hyperphenylalaninemia are now based on revised diagnostic criteria for PKU which are reasonably reliable but certainly not absolute.

At present, patients with persistently elevated serum PA can be divided into two groups: PKU and variants. PKU may be defined as patients with serum PA levels persistently greater than 20 or 25 mg. per 100 ml. and with the expected urinary metabolites of PA while ingesting an ordinary diet. All other patients with abnormal elevations of blood PA but without elevation of

blood tyrosine, are classified as variants.[23]

The incidence of PKU and the variant disorders has remained relatively constant in the United States, at about 1:13,000 live births.[24] The incidence of the variant disorders was estimated to be 1:50,000.[25] Hanley suggested that the ratio between variants and true PKU is 1:2,[26] although a recent report from Australia indicates that in some populations the ratio may be as high as 1:1.[27]

When a diagnosis of a variant form of PKU cannot be confirmed, the natural inclination would be to label the patient as having PKU and to treat, because of the poor prognosis in the typical untreated form of the disorder. Unfortunately, treatment of patients who have a variant form of the disorder with a restricted PA diet has resulted in diet-deficiency syndromes and even deaths,[28] an experience which has led to adverse criticism of the therapeutic regimen and of the prescriptive screening program in general.[1]

Although the consequence of misdiagnosis or inadequate diagnosis cannot be minimized, the positive aspects of the screening program appear to amply justify its continued application. If nothing else, screening programs have forced unproved concepts to be reevaluated and some to be rejected. Increasing numbers of children and some adults who are clinically normal but biochemically abnormal have now been identified.[23] An obvious direct and beneficial consequence of the PKU screening program has been the very early detection of infants with typical PKU. Although there is need for further validation of the long-term effects of therapy, it is generally believed that the prognosis for intellectual development is best with dietary treatment and also when therapy is started very early in infancy.[29]

Preliminary results of the current Collaborative Study for Treatment of PKU have indicated a 2:1 ratio of affected males to females in the first 90 newborn infants with PKU identified in the program.[30] This discrepancy from the 1:1 sex ratio in earlier reports has raised the question of whether female infants with PKU are being missed by the blood PA screening of newborns within the first few days of life. It is possible that a metabolic difference between infant males and females accounts for a lower neonatal rise in blood PA levels in the females. On the other hand, the unexpected sex ratio may be an artifact of small sample size. Other possible explanations have been offered, and further study is needed.

The genetic and biochemical implications, as well as the clinical correlaries of the variant forms of PKU are of interest. Shortly after the Massachusetts mass screening of newborns was started, Kennedy reported a series of atypical hyperphenylalaninemia patients whose serum PA levels were moderately high, but who were mentally normal or only mildly retarded despite lack of dietary restriction.[31] The ethnic background of this group of patients was largely Italian, in contrast to the northern European background most frequently associated with PKU. In a similar vein, PKU is exceedingly rare or non-existent in Ashkenazi Jews, although variants have been identified in this population group.[32]

The genetic and biochemical basis underlying the difference between the variant and typical forms of PKU remains unclear. Whether they can be attributed to mutations at different loci, or mutant alleles at a given locus or the effect of so called "modifier" genes requires elucidation. Justice and co-workers reported decreased liver PA hydrozylase activity in patients with variant

forms of elevated serum PA appear normal. They do not, as a rule, have seizures nor do they have abnormal electroencephalographic patterns.[23] This is decidedly different from untreated typical PKU patients in which as many as 75 to 95 percent have abnormal EEGs. Intellectually, the patients with variant forms of hyperphenylalaninemia seem to follow the distribution curve of the I.Q. for the normal population.

Although serum PA may attain levels of 30 to 40 mg. per 100 ml. in patients with the variant form on an ordinary diet, the blood PA levels are generally less than 20 mg. per 100 ml. The levels of urinary metabolites, which appear to be proportional to the elevation of serum PA, are also lower. An interesting but unexplained finding in these patients is the fluctuation in serum PA levels during a sustained high intake of this amino acid, suggesting that the variants have some adaptive mechanism, possibly an inducible enzyme or structurally altered PA hydroxylase rendered more stable by high substrate levels.[23]

As a result of the recognition of variant forms of PKU, investigators have been stimulated to look for causes other than elevated levels of serum PA to explain retardation in this disorder. On the one hand, the experimental and neuropathological findings which have been associated with elevated levels of serum PA[34] support a causal relationship between this biochemical abnormality and mental retardation. On the other hand, the reports of patients with normal intelligence who apparently have typical PKU cast doubt on this contention. Perry et al. described two siblings with identical elevations in their blood PA levels and characteristic urinary metabolites of PKU. One child was intellectually normal and the other profoundly retarded.[35] It

was postulated that the decreased plasma glutamine level in the retarded child may have been the factor responsible for the mental subnormality, since the concentrations of other metabolites and amino acids were comparable. Other studies do not support this hypothesis.[36]

Although there is no concensus in regard to therapy, most investigators suggest that dietary treatment be instituted if the serum PA level exceeds 20 mg. per 100 ml. on an ordinary diet. However, retarded patients have been observed with serum PA levels below 20 mg. per 100 ml.[18] Although it is possible that their retardation is not related to hyperphenylalaninemia, it is this type of inconsistency that makes it difficult to reconcile levels of PA and retardation. For this reason, many clinicians empirically treat all patients who have persistent hyperphenylalaninemia, regardless of severity. Recent studies by Levy and his co-workers suggests that persistent mild hyperphenylalaninemia of 2 to 12 mg. per 100 ml. in the untreated state does not lead to adverse effects on intellectual development or function.[37] Most clinicians would elect to treat patients with severe hyperphenylalaninemia because of the more substantial evidence that it leads to or is associated with mental subnormality. Unfortunately, after thirty-five years of intensive research, the cause or causes of retardation in PKU remain unknown.

Despite serious criticism of the research designs and interpretation of the data supporting the efficacy of therapy,[23] most clinicians appear to be convinced, from empirical observations, that PA restriction is of value, especially in infants treated from the early weeks or months of life. Nevertheless, criticisms of the evidence favoring dietary treatment appear to be valid and

are worth enumerating:

a. There is a selection bias in comparisons of treated and untreated groups. Untreated patients were first identified because of mental retardation, whereas most successfully treated patients were identified because of newborn screening programs or surveillance of newborns in families at risk.

b. In many studies there has been inadequate control of environmental factors, including the effects of rearing at home versus the institutions, the effects of the therapist's interaction with the child and other factors which can significantly alter the developmental progress of patients under observation.

c. In many studies, no distinction was made between the patients with typical PKU and the milder variants of this disorder.

d. Invalid comparisons have been made between developmental tests in infancy and intelligence tests at later ages.

e. Few, if any, "blind" studies have been carried out in which the investigators evaluating the development of a child were unaware of the therapeutic regimen under study.

At least part of the difficulty can be attributed to the fact that no single center has had a sufficient number of patients to make statistically valid comparison of the great number of variables leading to developmental differences. In response to the problem, a Collaborative Study of children treated for PKU was begun in 1967, involving 18 centers across the United States[32] and the results of this study are eagerly awaited.

At the present time, most clinicians would agree that it is mandatory that the diagnosis of PKU should be firmly established by studies of serum PA levels on an ordinary diet prior to the

institution of treatment. It also appears advisable to reserve therapy for patients whose serum PA levels are consistently above the 15 mg. per 100 ml. and that, as part of follow-up, patients should be restudied and challenged by tolerance tests or a normal diet to confirm the diagnosis and the need for continued treatment. This type of precaution is warranted because of the adverse effects encountered with dietary therapy, most of which have been attributed to PA deficiency. These complications include diarrhea, anemia, hypoproteinemia, bone demineralization, hypoglycemia, seizures and even death.[28]

Assuming PA restriction is important for patients with significant hyperphenylalaninemia, no information is available about the duration of therapy necessary for optimal results. Since brain growth, as reflected by head circumference, approaches 90 percent of adult size by six years, and myelinization is also nearly completed by that time, some investigators have felt it unnecessary to continue therapy beyond that age.[23]

The question of the duration of dietary regulation raises a more critical issue for females with the disorder than for males. A number of families have now been investigated for the effect of maternal PKU upon the children of such mothers.[39] It is clear that most of the offspring born to these affected women are mentally retarded, regardless of the genotype or biochemical phenotype of the infant. It is presumed that exposure of the fetus to hyperphenylalaninemia during gestation is harmful to the development of the fetal nervous system and this assumption receives support from animal experimentation.

If maternal PKU is harmful to the fetus, one of the legacies of current screening and treatment

programs will be the need to develop programs for the recognition and management of maternal PKU homozygotes during their pregnancies. The example of maternal PKU is only one of the many possible situations in which early screening followed by treatment can result in an increased prevalence of "healthy" mutant homozygotes who may expose their progeny to certain risks during intrauterine life, regardless of the fetal genotype. It is important, therefore, to assume that the patient is well informed about her disorder, including the possible hazards to her progeny if care is not exercised during pregnancy. Some investigators consider such measures insufficient and, in order to protect children born to such women, they advocate that a registry of women with mutant genotypes be maintained.[40] In addition, prescriptive screening of mothers in early pregnancy, or of women during childbearing ages prior to pregnancy, has been suggested as a means of providing additional safeguards for identifying pregnancies at risk. Clearly, prescriptive screening carries with it implications and even obligations that extend well beyond the early neonatal period of life.

Since disorders other than PKU can result, if untreated in severe disability, mental subnormality and death and since therapy, if started early, is sometimes effective, should we consider mass screening for these disorders, some of which are listed in Table 4? Unfortunately, our knowledge of these conditions is even less complete than that for PKU. In many instances, there is insufficient information about the range of clinical manifestations and the history of untreated disease. Moreover, the effectiveness of treatment and the benefits of early diagnosis often remain to be demonstrated. In many of

these disorders we do not yet know how successful proposed mass screening techniques would be in avoiding false negative tests or too high a proportion of false positive tests which require follow-up. Most infants with classical galactosemia would be actually ill, or even dead, as experience has shown[41] by the time the results of a screening test done in the first week of life or later become available. Similarly, by this time, the majority of children with maple syrup urine disease would already be irreversibly damaged.[42]

The need clearly exists for more information about the inborn metabolic errors prior to the introduction of prescriptive screening. On the other hand, there is ample justification for further research and pilot programs dealing with the detection and therapy of these disorders. A number of studies along these lines are underway in this country and abroad[43] and the cumulative results of such studies will provide information not only about the natural history of these disorders but also about their incidence.

5. Methods for Detecting Inborn Errors of Metabolism.

In searching for inborn errors of metabolism, we must be aware of the pitfalls and errors met with in this as in any other field of clinical chemistry. For example, abnormal amino acid patterns are found in blood and urine in many disorders other than the inborn metabolic errors.[44] Artifacts may be produced by diet or drugs. Sample deterioration or the use of unsatisfactory reagents may lead to cases being missed. The provision of detailed information about the patient and care in the collection, preservation and transport of samples is, therefore, mandatory.

The bacterial inhibition assay of Guthrie is one of the most widely used techniques in mass screening for a variety of inborn metabolic errors.[45] Similarly, one-dimensional chromatography of amino acids, or their derivatives, and of carbohydrates is still commonly employed, as it is a method within the scope of almost all clinical laboratories. Chromatographic separation is usually carried out on paper, but this layer chromatography[46] and high voltage electrophoresis[47] are increasingly preferred because of the more rapid and sharper separations which can be obtained by these methods. When more detailed information is required, separation can be carried out by two dimensional chromatography on paper or thin layer plates. Other, more recent techniques proposed for separation and identification or urinary and blood metabolites include column chromatography,[48] gas-liquid chromatogrpahy,[6] and automated biochemical assays[49] although none of these methods is yet suitable for mass screening purposes. It should be borne in mind that simple screening methods such as the ferric chloride or nitro prusside spot tests, and tests for reducing substances in urine can be carried out as part of routine medical care in the clinic or office and these may be useful in case detection.

6. Potential Areas for Screening.

a. Other Metabolic Disorders. Recent studies of umbilical cord cholesterol levels have indicated the practicability of diagnosis of neonatal hypercholesterolemia in infants born to families known to have Type II hyperlipoproteinemia.[50] The importance of the earliest possible diagnosis of this disorder is underscored by the fact that cholesterol and β-lipoprotein cholesterol levels can be reduced to normal or near

normal by diets low in cholesterol, rich in polyunsaturated fats and coupled with Atromid^{R} or Cholestyranine^{R} therapy.[51] Early diagnosis and early treatment of familial Type II hypoproteinemia in the neonate should then offer hope in prompt normalization of cholesterol levels and prevention of the associated premature atherosclerosis.[52]

b. Screening for Heterozygotes. Most of the inborn errors of metabolism are inherited as autosomal recessive disorders, in which a pair of mutant alleles at a single gene locus are required for clinical expression of the trait. Since the apparent frequency of the homozygous forms of such disorders is rare, vast numbers of normal tests must be performed in order to find a single homozygous patient with a particular disease.

On the other hand, the frequency of positive results would be greatly increased if it were possible to test for the heterozygote. For example, the frequency of PKU heterozygotes in the population is approximately one in 50. Thus, from a statistical viewpoint, it is considerably more rewarding to search for heterozygotes. When the carrier is identified, one can then carry out further studies on the selected pedigree.

Although there are several features which make screening for the heterozygote attractive, there are also many drawbacks. Heterozygotes rarely exhibit significant deviation from normal in the concentration of the relevant metabolite, contrary to the findings in the homozygous deficient subject. Frequently, the overlap between normal and carrier subjects is large enough that a single measurement of the metabolite in blood or urine would not discriminate the heterozygote with any reliability.

One can attempt to circumvent the biochemical equilibrium sustained by the single normal allele by stressing the capacity of the particular metabolic pathway. These tests are usually carried out as substrate loading tests and are not suitable for general screening purposes. Assay of the gene product itself, such as the activity of an enzyme in red or white blood cells, serum, tissue samples or urine, is often reliable and convenient for ascertaining the heterozygote. In most of the genetic autosomal metabolic disorders, there is a predictable gene dose-effect in which the concentration of the gene product is approximately half normal.

Screening of high risk populations for heterozygous carriers may be justified. For example, Tay-Sachs disease occurs in about one out of every 5,000 births among Ashkenazi Jews in this country.[53] The frequency of the mutant gene is .015 and the prevalence of carriers in this population is about one in 30 individuals. Since the carrier for the Tay-Sachs mutant allele can be easily detected by a decrease in serum hexoseaminidase "A" activity,[2] it may be of value to screen Jewish couples prior to marriage or childbearing, particularly if there has been a history of Tay-Sachs disease on either side of the family.

Screening for heterozygous carriers has been useful in areas which have no direct bearing on genetic counselling or the identification of families at risk for having affected progeny. Thus, identification of the carrier has been helpful in confirming the mode of transmission of certain genetic disorders[54] as well as in demonstrating the esistence of genetic heterogeneity for several of the inborn metabolic errors.[55] Moreover, studies of the frequency of heterozygous carrier states have been helpful in

estimation of the frequency of various mutant genes among different populations.[56]

In conclusion, therefore, screening for inborn errors of metabolism should have two main objectives. It should be able to discriminate simply and reliably between those who have a disease or trait and those who do not; and early detection of such individuals should provide an opportunity to gain an advantage from treatment. The criteria previously enumerated for validation of screening procedures on a mass basis suggest that, in our present state of knowledge, it is doubtful that these particular objectives can be fulfilled for a majority of the inborn errors of metabolism.

Although the primary role of screening would appear to be preventive, there are other desirable objectives which continue to provide the major stimulus for development and use of these programs in the community. Screening permits early detection of poorly understood diseases and provides an opportunity to study them and to elucidate their pathophysiology. Moreover, previously unknown problems may be discovered and furnish better insights into the ecology of human biochemical processes in health and disease.

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Table 1

TARGET OF SCREENING TESTS

1. Level of the Gene Product
2. Level of the Metabolic Intermediates
3. Level of the Clinical Phenotype

Table 2

EXAMPLES OF "FALSE POSITIVE" RESULTS IN MASS SCREENING

Finding	Primary Disease Target	Alternative Causes For Positive Tests
Hyperphenylalaninemia	Classic PKU	a. Atypical PKU b. Variants of PKU c. Transient hyperphenylalaninemia
Hypertyrosinemia	Hereditary hypertyrosinemia	a. Neonatal tyrosinemia b. Severe hepatic disease
Hypervalinemia	Branched-chain ketoaciduria (BCKA)	a. Valine transaminase deficiency b. Intermittent BCKA
Hypermethoninemia	Homocystinuria	a. Transient hypermethoninemia in newborn b. Severe hepatic disease

Table 3

GENERAL PRINCIPLES IN SCREENING FOR INHERITED METABOLIC DISORDERS

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1. Screening test must be effective, simple, easy to perform; test samples stable during transport to laboratory.

2. Screening test must be oversensitive, with no or few false negatives.

3. Means at hand for prompt study of all suspected cases.

4. Effective treatment for disorder available.

Table 4

INBORN ERRORS OF METABOLISM CONSIDERED FOR MASS SCREENING

Homocystinuria

Histidinemia

Maple syrup urine disease

Tyrosinemia

Galactosemia

Lysinemia

Mucopolysaccharidosis

DISCUSSION

SALLY KELLY (New York State Department of Health, Birth Defects Institute, Albany, New York): I think that the geneticists today are in the same state that virologists were in the 1950's. At that time all viruses were thought to be bad. But then the echo viruses were discovered which were nick-named the "viruses in search of disease" and I might suggest that we consider Dr. Nitowsky's variance of phenylalaninemia as an "enzyme defect in search of a disease".

HEREDITARY ANEMIAS IN SOCIETY AND PROSPECTS OF PREVENTION*

Robin M. Bannerman

INTRODUCTION

On a world wide basis hereditary forms of anemia are immensely common and affected persons are to be numbered in millions. They present at least two important problems to society. One is the impact of the severe forms on families and in societies in areas where they are common, in terms of human suffering, medical needs and economic burdens. Another concerns possible approaches to reducing the numbers of new severe cases by the detection and counselling of heterozygotes.

The anemias to be considered are the thalassemias and sickle cell anemia and, to a lesser extent, the Hb C and E diseases (Table 1). These conditions have it in common that they exist in populations in two possible forms. The vast majority, the heterozygous carriers, are generally symptom free, not anemic and not aware of their carrier status. The far fewer homozy-

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* Studies supported in part by a WHO Exchange of Research Workers Grant, United States Public Health Service, Special Fellowship HE-49915 and New York State Birth Defects Institute, Contract Number 90221.

gous or doubly heterozygous patients are generally anemic, often severely, and obviously disabled. Their life span may be anything from zero, as in the case of alpha-thalassemia hydrops fetalis, to relatively normal. On the average, it is so short that they may be regarded as genetic lethals, or sub-lethals, and affected individuals will contribute few offspring to the next generation.

Earlier in the Symposium some aspects of the subject, such as the effects of genetic counselling at the population level,[1] and the use of screening programs,[2] have already been touched on. The approach in this paper is a clinical one, starting with a brief review of the conditions listed in Table 1. G6PD deficiency was omitted for lack of space but should be kept in mind as another source of disability in some populations.

HETEROZYGOUS FORMS

Among the heterozygous states, the β-thalassemias, occurring chiefly in people of Mediterranean ancestry, present at least 5 subtypes.[3] The carriers are generally symptom free and not anemic but the spectrum includes occasional individuals with a moderate degree of anemia and splenomegaly and abdominal pain due gallstones and splenic infarction, ankle ulcers and other features may occur. Alpha-thalassemia is perhaps the most benign in heterozygous form since it may only be detectable in cord blood, at least in what is now called alpha-thalassemia$_2$.[4,5,6] The phenotype at birth includes the presence of a slight excess of Bart's hemoglobin in cord blood, with mild red cell changes which tend to disappear in childhood. The Negro children in Baltimore in whom the diagnosis was

made at birth,[7] minor red cell changes could still be detected in childhood and hemoglobin synthesis studies have shown a possible continued alteration of the alpha-beta chain labeling ratio.[8] Alpha-thalassemia$_1$ is associated with slightly more hemoglobin Bart's in cord blood and with more easily detectable changes in adult life, including the presence of very small amounts of Hb H. This is to be distinguished from Hb-H disease which is probably a doubly heterozygous state associated with moderate anemia, splenomegaly and occasional other complications.

For sickle trait there is a slight paradox, because population and statistical evidence suggest that it is not deleterious and implies that S trait individuals have a normal life expectancy (reviewed by Harris and Kellermeyer, Ref. 9). In Jamaica, a recent careful population study indicated that sickle trait adults had no greater a tendency to show morbidity from a number of chronic conditions than did the rest of the population.

On the other hand, at the level of individual patients, there is the knowledge that sickle trait is not a wholly innocent condition. However, the dramatic clinical events, such as splenic infarction following high altitude flight in non-pressurized aircraft,[9] and the recent report of four young soldiers who suddenly died after arduous exertion during training at an altitude of 4,000 feet,[11] are isolated instances. While such instances should lead to consideration of screening groups of people who may be at special risk, they should not be allowed to alarm the huge majority of symptomless S trait individuals. Finally, Hb C and E traits also do not appear to cause anemia or other clinical disability.

HOMOZYGOUS FORMS

Alpha-thalassemia hydrops, relatively recently elucidated in Southeast Asia, is probably the homozygous state for alpha-thalassemia$_1$.[12] Affected infants survive through fetal life but are stillborn or die within minutes of birth. The fetus is congested and shows the most intense erythropoietic over-activity, so that almost all tissues are a site of erythropoiesis, including endocrine glands, skin and intestine.[13] This erythropoietic activity is largely ineffective, since the major hemoglobin component is hemoglobin Bart's with some Hb H, and both of these hemoglobins are useless for oxygen carriage. It would appear that the fetus limps through pregnancy using an embryonic type of hemoglobin, probably Hb Portland, as its main oxygen carrier, but that this is inadequate to sustain postnatal life.[14] At least one infant has been treated by exchange transfusion but this was unseccessful and could have been of transient benefit only, since the organism is apparently totally unable to synthesize alpha chains and, therefore, cannot make either fetal or adult hemoglobin.[15] Treatment of this state, if it ever became desirable or practicable, would have to depend on approach at a genetic rather ehan a hematologic level. Meantime, the disease is too lethal to be a continuing burden to the family but must be a source of terrible distress to the mother particularly when it occurs repeatedly in successive pregnancies.

Cooley's anemia, the homozygous state for β-thalassemia, is better known, presenting the syndrome of severe anemia, small stature, bone deformity and jaundice. It may arise from the homozygous state or doubly heterozygous state of at least five kinds of β-thalassemia mutation.[3,16]

Generally, the diagnosis is made in infancy and survival usually, but not always, depends upon regular or at least intermittent use of blood transfusion plus other supportive treatment. As a result of the development of such treatment, the survival of these patients has changed remarkably during the last 20 or 30 years. Silvestroni has pointed out that in Italy, before Thalassemia Centers (Centro di studi di micro-citemia) were developed, most patients died before the age of 5 years. Now most survive through adolescence and beyond 17 (Figure 1).

This situation is summarized in a sketch (Figure 1). Such a form could, of course, be used to represent what has happened in many childhood diseases, including, for instance, cystic fibrosis. No one would wish to deny transfusion treatment to these children where it can be made available. Likewise, once transfusion treatment has been started, it would be a very hard decision to stop it. Yet, the patients are often literally kept alive by blood transfusion. What is the effect of this on the child, the family and society? Even with devoted care, the child has tended to live a limited and sheltered life, with peaks of well-being after transfusion and troughs of fatigue, weakness and distress before transfusion or in such complications as severe infections, pathologic fractures and other troubles. Some patients manage to remain reasonably content, to enjoy school and social life, but some become withdrawn, defensive and petulant as they grow up, knowing or sensing their ultimate prognosis. The use of higher transfusion regimens is improving the immediate situation, however. For the family, it often means that all family plans rotate around the affected child, sometimes two children, and the rhythm of regular transfusion.

Sometimes the situation may be even more disruptive for the family. For instance, families in Cyprus having a child with Cooley's anemia used to emigrate to London to ensure that the affected child would get regular transfusion treatment. The medical burden, where cases are few, as in this country, is perhaps not so serious but it may be very great in other places.

There are at least 10 Thalassemia Centers now in Italy. The one in Rome has some 200 patients and the clinic at Naples has approximately 100. Each patient is receiving on the average 2 units of blood about every 6 weeks. This would imply that the annual blood consumption by the Rome clinic might be 3,200 units. For comparison, a 600 bed general hospital in the U.S. uses about 4,000 - 5,000 units per annum, including open heart surgery and dialysis. Thus, a major clinical burden has been shouldered and by its very success it is a burden which continues to grow. The financial cost of transfusion maintenance may be considerable,[18] yet, as was pointed out earlier in the Symposium, how can a satisfactory balance sheet of benefit versus costs be drawn up? The burden will not grow where it cannot be shouldered and in areas where such forms of treatment are not available, the patients with Cooley's anemia will continue to die very young. This must be what occurs in Southeast Asia and also in some parts of the Mediterranean.

Finally, sickle cell anemia is certainly the best known of these diseases. It is generally less severe than Cooley's anemia and compatible with survival into adult life and with reproduction, though the overall fitness of sickle cell anemia patients must be considerably lower than normal. Few of the patients live a normal

life. Their schooling is frequently interrupted by hospital admissions. One patient, just graduated from high school, has already had 16 hospital stays and innumerable outpatient visits in his lifetime. He cannot manage any heavy job and yet has not acquired appropriate skills for other jobs in a competitive labor market. In many senses then, such a patient is going to need from his family and from society continued personal, medical and economic support. The patients generally do not require regular transfusion though some will need intermittent transfusion. Their survival could be represented on a similar curve to that shown in Figure 1, though it would be of slightly different shape. One might guess from the data of the literature and personal experience that the average survival is less than half that of normal individuals - in areas where there are reasonable standards of medical care. In other areas many patients with sickle cell anemia will die in infancy, forming a part of overall infant mortality. This is probably still the case from some parts of Africa and presumably is the reason why it was once said that sickle cell anemia (as opposed to trait) was very rare in Africa.

TREATMENT OF HOMOZYGOUS FORMS

In the present state of the art, treatment of these syndromes is symptomatic only and the results could reasonably be called poor. What are the prospects of treatment at or near the level of the gene? While the most drastic forms of genetic engineering are still speculative, one approach which is relatively more plausible, would involve tampering with the "switching" mechanism. In sickle cell anemia, for instance,

this might require that one or both of the mutant beta chains be switched off or never switched on and adequate gamma chain production be stimulated to continue. Theoretically, this is a relatively hopeful line of approach, since there are precedents in which unusual switching events seem to have occurred; for instance, elevated F hemoglobin may appear in rare cases of leukemia. Similar, but more difficult arguments, might apply in thalassemias.

Can sickle cell anemia be diagnosed in utero? Probably yes, late in pregnancy, too late to be useful, but there are tentative suggestions that early diagnosis might be feasible from fetal blood obtained before the 12th week - though obviously there are formidable technical difficulties. At this stage it would, of course, be practicable to consider the termination of pregnancy if the diagnosis were certain.

In post natal life, it has been suggested that a sample of the patient's own bone marrow might be removed and in some fashion transformed and then returned to the patient to produce a line of more normal red cells - but this is certainly in the realm of speculation. Bone marrow transplant from a normal individual has often been advocated. It has been attempted in at least 6 cases of Cooley's anemia,[19] without success, but also without harm to the patients. They were probably inadequately prepared, since people have not yet been quite willing to grasp the nettle of first totally destroying the host bone marrow with its normal white cell and platelet production.

WORLD INCIDENCE

Knowledge of world distribution is mostly in terms of frequency of heterozygotes, as deter-

mined by population surveys of S trait, β-thalassemia, C trait and E trait from tests of adult blood and of α-thalassemia from tests of cord blood. Parts of the works, such as Italy, Greece and some areas of Africa and Southeast Asia, have been relatively well mapped by surveys. For other parts of the works, including other areas of Africa and Asia, mainland China and southern Russia, we have only fragmentary information. The disorders do not occur to any significant degree in indigenous inhabitants of the Americas. Population data is reviewed in several places, including a recent WHO report;[20] an extensive compilation is to be found in Livingstone's book.[21] No estimate of the total number of carriers in the whole world will be attempted here, but it would have to be expressed in hundreds of millions and would represent a significant fraction of world popu-population.

Some examples will be considered, starting with sickling (Table 2). The problem nearest to hand is sickling in the Negro population in the United States. Of a total U.S. Negro population of approximately 19 million, 8% are heterozygous for hemoglobin S. It follows that about one thousand births per annum will be new cases of sickle cell anemia. They will be arising, however, from a relatively small number of marriages, only 1/156, or approximately 6 per thousand, will be marriages between two sickle trait individuals. The table shows similar calculations for a few other countries.[20,21] In Nigeria, with a total population of over 55 million, the sickle trait frequency ranges from 18 to 40% (Table 2). Assuming an average of 25%, there will be 14 million heterozygotes. This time, 1/15, or 6 per hundred, marriages are likely to be between heterozygotes and there

will be approximately 62,000 new cases of sickle cell anemia per annum. Other examples, chosen because data are easily accessible, are the smaller countries of Ghana (where there is also a high frequency of Hb C), Chad and Togo but there are some 35 African countries in which there is a very significant frequency of sickling. They make up a total population of over 250 million and, at a rough estimate, there may be 30 million sickle cell trait carriers in all of them.

Considering β-thalassemias, the situation in Italy has been relatively well studied, particularly by Silvestroni and his co-workers (Table 3). Because of striking variations in frequency over different parts of Italy, it is difficult to generalize effectively for the whole country. However, Silvestroni has estimated himself that there are some 2 million β-thalassemia heterozygotes in a total population of 50 million and that 1,000 new cases of Cooley's anemia are born per annum.[18] Table 3 shows some specific examples. One of the highest frequencies is in Cagliari, the capital of Sardinia. Marriages between two carriers of the trait will be 1/18 and 262 new cases of Cooley's anemia will be expected per annum. At Ferrara, famous in the history of thalassemia, 1/52 marriages will be expected to involve two heterozygotes. The problem is similar in Greece (for recent population data, see Ref. 3).

Alpha-thalassemias and Hb E deserve mention because of their remarkable frequency in Southeast Asia.[22] The data from one cord blood study in Thailand[6] demonstrates (Table 4) the fact that one-third of all cord bloods are abnormal, revealing over 10% E trait, a total of 15% α-thalassemia trait alone and another 3% α-thalassemia accompanied by Hb E and a

significant number of Hb H. Given that Thailand has a population of 30 million and the neighboring countries of Burma, Cambodia and Laos - which probably have similar gene frequencies - have a further 30 million, this is a total of carriers and expected incidence of severe cases which certainly approaches the sickle cell anemia problem in Africa.

MAINTENANCE OF GENE FREQUENCIES

The traits discussed are regarded as balanced polymorphisms and their high gene frequencies are generally attributed to the selective pressure of malaria.[20,21,23] Although full details of the processes are not yet clear, Luzzato and co-workers from Ibadan[24] have demonstrated that parasitized cells from AS individuals sickle more readily than non-parasitized, probably leading to more effective destruction of the parasites by phagocytosis. There may well be other factors in selection and there are indications of complex interactions where two or more traits co-exist in the same population. Malaria is now non-existent in North America and in the Mediterranean area generally, certainly in Italy. Thus, this particular selection pressure will have been relaxed and the gene frequencies for thalassemia in Italy and sickling in U.S. Negroes will be expected to fall towards equilibria at new low levels. In many parts of Africa and Southeast Asia, however, malaria is still far from controlled and it may be many years before malaria is generally eradicated. But in due course, the same effect, a fall in gene frequency, will be expected in these countries also.

POSSIBLE LIMITATION OF HOMOZYGOTES

Meanwhile, new homozygous cases will continue to appear. It is evident that if heterozygous individuals did not marry each other or, having married, did not produce children, then the appearance of new homozygous cases would practically cease. It is important to consider the possibilities and limitations of programs which might seek to achieve this result, including whether they would work, whether they are desirable in one place or another and some of the practical considerations involved.

The experience of the Thalassemia Centers in Italy is of importance. Their program was limited some 15 years ago.[18] The proposal was that in areas of high frequency for β-thalassemia, children would be tested in high school by an appropriate screening test and those found to show evidence of β-thalassemia would be given an appropriate card. The card states explicitly that the bearer carries a minor hereditary red cell anomaly which is not in itself a source of illness, but that if the bearer should marry another carrier of the anomaly then there would be a serious risk of having a child "doomed to die from an incurable blood disease". An accompanying educational campaign was a part of the program. The need for education has been demonstrated by at least one specific enquiry; in the Ferrara region it was found that the population in this area of high thalassemia frequency generally had a superficial and incorrect understanding of the inheritance, and viewed its existence in the family as a source of shame to be concealed.[25]

At first sight, this would seem to be a workable scheme and it has apparently been continuing in operation, at least in some areas. Unfortu-

nately, no system of follow-up, to monitor the effectiveness of the program, was incorporated and there is no information, other than anecdotal, to show that it has an effect.

To demonstrate that such an effect can be observed, the results of a small study carried out in Buffalo can be cited.[26] It had been noted that the number of young children with Cooley's anemia was less than would have been expected from the known frequency of β-thalassemia minor in the population of Italian origin in Buffalo. An apparent decrease in incidence was documented by study of hospital records as shown in Table 5. Because numbers are so small these have been grouped in five-year periods. Although no new cases of Cooley's anemia had been recorded in and around Buffalo for the last five year period, a new case has just been diagnosed in an infant, the first child of a couple in whom the diagnosis of thalassemia minor was known and who had been warned by their family doctor of the risk.

The most obvious explanation for the apparent decline comes from a study of marriage announcements (Table 6). Although shifts of population complicate interpretation, a comparison of the years 1940 and 1960 shows a fall in the number of marriages of Italian to Italian and an increase in the number of marriages between Italian and other. This is a simple numerical expression of the melting pot phenomenon which is so much discussed but which is actually so slow and incomplete. Although the semi-isolate is breaking down, in the sense of marrying more outside the ethnic group, marriages are still largely within the same religious group since most of the "other" names appear to be of Polish and Irish origin and, therefore, probably Roman Catholic. As an almost accidental result of

social change, the incidence of a serious sub-lethal genetic disease has fallen. If this can happen by accident, should we not consider whether it could be induced to happen also by design?

PRACTICAL ASPECTS OF PREVENTION

To achieve this by design, it would, of course, be necessary to detect heterozygotes. Prematrimonial testing is too late and the ideal age might be at 15, in high school. Around this age would seem to be particularly strategic, with an accessible population, which is educable and generally not yet committed to a marriage partner. As to methods, for sickling a variety of new screening procedures are now being elaborated and advocated. Perhaps the most promising is the use of electrophoresis from dried blood spots,[27] which would not only obviate the need for venepuncture or for tests on fresh blood, but would also allow detection of Hb C carriers and, perhaps, β-thalassemia with elevated hemoglobin A_2.

Detection is only the very first step and to set up a detection program without a sophisticated and effective follow-up would be mischievous. The second step would involve the means to inform the heterozygotes of the risks undergone to prospective offspring in marrying another heterozygote. Certainly a card could be issued, but this by itself is by no means certain to be effective and it requires a suitable and extensive educational program given by people and in a form acceptable to the population under consideration. Having theoretically achieved these two steps, there is at least a third and that is a means of determining whether such counselling has had an effect, and this would

have to be planned on a longer term basis. It could best be done by means of relatively automatic record linking processes (as used, for instance, in the record linkage in the Oxford region of England), which could automatically score the marriages of people who had previously been tested and subsequently score the health records of the children of such marriages. This presupposes relatively deliberate and stable patterns of living, mating and reproduction in the population, which are not always necessarily present.

Such a program would attempt to interfere with the randomness of mating, which, of course, is not random in any case. But it would want to "head off" only a surprisingly small proportion of all marriages (see Table 2 and 3). There is probably a certain range of population frequencies and heterozygote mating frequencies which would be most profitable, as it were, to consider, perhaps, in the range 1 in 20 to 1 in 300 marriages in the population. This does not sound too formidable. Arranged marriages, in which the partners have no real choice, are the rule in many parts of the world and many people would be astonished to think that they should have a totally free choice of marriage partner. This recalls the words of Dr. Samual Johnson, who said, "Marriages would, in general, be as happy and often more so, if they were all made by the Lord Chancellor."

Finally, the ultimate effect of such a program on gene frequencies is uncertain. If the selection pressure (e.g. falciparum malaria) remained the same, then an increase in gene frequency would be probably. However, it is unlikely to remain the same, so that a slow decrease in gene frequency is more likely in the long run, to reach a new equilibrium level,

determined largely by the mutation rate.

CONCLUSION

1. If all heterozygotes for the disorders discussed ceased marrying other heterozygotes, the incidence of the lethal or sub-lethal forms would decrease and much human suffering and associated social, medical and economic burdens would be reduced.
2. The effect has come about by accident in at least one small focus of β-thalassemia - doubtless in others, too.
3. To achieve such an effect, if it is a desired effect, would require a sophisticated and long-term program in which the detection of heterozygotes is only the first and easiest step, and the counselling and follow-up phases are equally important.
4. Whether physicians and medical geneticists should advocate such programs is debatable and opinions range from the evangelical to the cynical. There must be a reasonable middle way, and in areas of appropriate standards of medical care and educational sophistication, a screening and counselling program which included the safeguards mentioned above, would be justifiable. Two such areas are those parts of Italy with much thalassemia, where such a program already exists, and in the U.S. among Black Americans with sickle trait.

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Table 1

Hereditary Anemias

Heterozygous states (generally no disease)

β-Thalassemia trait (5 subtypes) (Italy,Greece)

β-Thalassemia trait (2 or 3 subtypes) (S.E.Asia)

Sickle trait (Africa)

Hb C trait (W.Africa)

Hb E trait (S.E.Asia)

Homozygous or doubly heterozygous states
(Generally severe disease; genetic lethals or sublethals)

β-Thalassemia hydrops fetalis

Homozygous -thalassemia

Sickle cell-thalassemia

Sickle cell anemia

Hb SC disease

Hb E-thalassemia

Table 2

Sickling - Some Examples

Population	Number	S Trait %	Incidence of Homozygous	S Trait x S Trait Marriages
Nigeria	55×10^6	25	62,000	1/15
Togo	1.6×10^6	23	1,500	1/18
Chad	2.8×10^6	20	1,800	1/24
Ghana	7.3×10^6	15	2,500	1/44
U.S. Negro	19×10^6	8	1,000	1/156

Table 3

β-Thalassemia - Some Examples (Italy - based on Silvestroni)

Population	Number	β-Thal. Trait %	Incidence of Homozygous	Trait x Trait Marriages
Cagliari	755×10^3	23.85	262	1/18
Ferrara	419×10^3	13.46	27	1/52
Catanzaro	696×10^3	10.31	38	1/94
Cosenza	655×10^3	7.24	20	1/190
Palermo	1130×10^3	4.27	8	1/555

Table 4

Cord Blood Hemoglobin Abnormalities in Thailand*

Hb Types	Designated Genotypes	%
A + F + E	Hb E trait	10.86
A + F + Bart's (small amount)	α-Thal$_1$ trait	8.45
A + F + Bart's (trace)	α-Thal$_2$ trait	7.95
A + F + E + Bart's (trace)	α-Thal$_2$/Hb E	2.06
A + F + E + Bart's (small amount)	α-Thal$_1$/Hb E	1.35
A + F + Bart's (moderate amount)+	α-Thal$_1$/a-Thal$_2$	0.36
Others (including supposed β-Thal. trait, homozygous E, etc.)	----	0.56

*From data of Pootrakul et al., 1970.

+Assumed to represent Hb-H disease.

Table 5

Patients with Cooley's Anemia in Western New York

Year of Birth	Number
1946-50	8
1951-55	7
1956-60	5
1961-65	2
1966-70	0

(Based on Ingall et al., 1969, ref.26)

Table 6

Marriage License Applications in Buffalo, New York

	1940		1960	
	Number of Couples	%	Number of Couples	%
Italian marrying Italian	503	8.8	269	6.5
Italian marrying non-Italian	366	6.4	530	12.8
Total (all marriages)	5,708	100.0	4,141	100.0

(From Ingall et al., 1969, ref. 26.)

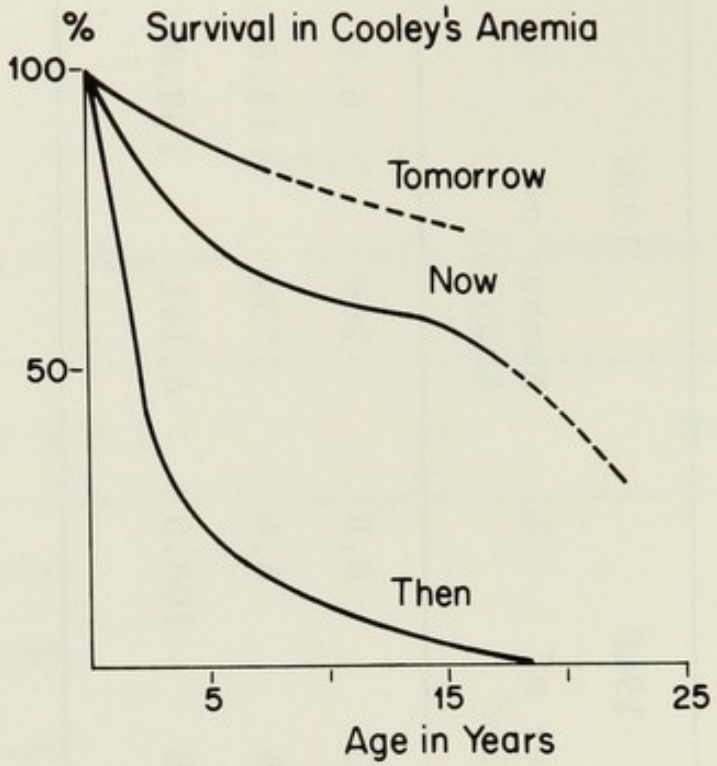

Figure 1. Diagram to show the trends of changing mortality in Cooley's anemia; a similar diagram could be used to represent the situation in a number of other childhood diseases.

DISCUSSION

DR. MURPHY: I wonder if you have any information about the genetic fitness of, for example, the heterozygote of sickle cell disease.

DR. BANNERMAN: I don't know. There are figures for the fitness of patients with sickle cell anemia and it is quite low.

JOSEPH ROBINSON (New York State Department of Health, Albany, New York): Dr. Bannerman, can you explain the signs and symptoms in patients with the trait brought about by excessive stress by athletes or patients undergoing operations?

DR. BANNERMAN: There are at least three situations in which people with the trait may have symptoms: flying, or going to high altitudes without extra oxygen, general anesthesia and pulmonary illness, and possibly extreme stress. The common factor is hypoxia and the trouble is not anemia but infarction. These are rare complications among the one and a half million carriers in the United States. Nevertheless, I have seen a number, including bone, lung and brain infarcts, all occurring in patients with sickle trait and precipitated by stressful situations.

VIRGINIA APGAR (National Foundation-March of Dimes, White Plains, New York): I cannot help but put in a word for the anesthesiologist. In almost all conditions except for rare anesthetic accidents, patients breathe much more oxygen when anesthetized than we do right here.

DR. BANNERMAN: Thank you, Dr. Apgar. I'm sure you're right but would you not agree that the

that the anesthesiologist would like to know it the patient had that trait, or doesn't it matter?

DR. APGAR: Oh, yes.

ETHICAL ISSUES RAISED BY ADVANCES IN GENETICS

Charles Carroll

The ethical issues raised by advances in genetics are, at bottom, the same that accompany any new discovery by man. Whether or not these advances will prove as important as the discovery of fire, the wheel or the theory of relativity is irrelevant. The historical continuum lies within the time space continuum. And if history has anything to teach us, it is the ambiguity of progress, the ambiguity of freedom and the ambiguities of life.

THE AMBIGUITY OF PROGRESS

We who were born "in this century, tempered by war, disciplined by a hard and bitter peace, proud of our ancient heritage"[1] rejoiced at the discovery of the airplane and Lindbergh's solo flight to Paris - and lived to shudder at reports of the bombings of Rotterdam, Coventry and Dresden.

We who relished every new technological development and the creature comforts which our mass production economy provided us - lived to see pictures of the horror of Auschwitz, Buchenwald and Dachau.

We who reveled in every new scientific gain - lived to share the gnawing after-thoughts of Max Planck, Otto Hahn, Albert Einstein and J. Robert Oppenheimer once the atom had been

split and the bomb had exploded in the skies over Hiroshima and Nagasaki. And now we witness the anxiety of Max Born in 1968;[2] J. Shapiro of Harvard in 1969;[3] and James D. Watson, co-discoverer of the double helix, in 1970[4] about the present day drift in the physical and life sciences.

We who judged at Nuremberg - have lived to ask with General Telford Taylor, the United States' Chief Counsel at the War Crimes and Doctors' Trials, if judgment at Nuremberg has not become judgment by Nuremberg?[5]

We can no longer pretend that the spatio-temporal is entirely ahistorical. We cannot step outside the historical continuum. We cannot dismiss the past and start from wholly new beginnings. We can no longer delude ourselves with the thought that progress is inevitable - or an unmixed blessing.

To subsume the 5700 years old history of Israel, the 2600 years old history of Greek thought and the 2000 years old history of Christianity in the "now" and the "now" in the "future " is an interesting attempt at an intellectual tour de force. But to pronounce the demise of the ethic which sprang from that tradition (as the California Medical Association thought it had in its official journal in September, 1970) is premature. Without devising or even attempting to devise an ethic to take its place, the announcement would be comic in its niaveté were it not so tragic in its implications.[6]

We cannot dismiss our civilization's emphasis upon the individual and insist upon emphasis upon the species as if we were calling for the abandonment of a century old or even Christian tradition. The editors of The Jerusalem Bible in their "introduction to Job" have written of post-exilic times as an age when already "absorption

in the destiny of the nation as a whole was giving way to an interest in the individual."[7]

We cannot confuse law with public opinion or the law of nature with natural law. As Werner Jaeger has written: "A 'law of nature' is merely a general descriptive formula for referring to some complex of observed facts, while Heraclitus' divine law is something genuinely normative. It is the highest norm of the cosmic process, and the thing which gives that process its significance and worth."[8] Call it the divine law as Heraclitus, the "general law" as Aristotle,[9] the "law (of) right reason" as Cicero,[10] the "natural law" as St. Thomas Aquinas,[11] it is that very same of which Adalbert Stifter wrote and Dietrich Bonhoeffer read in prison - "the terrible majesty of...which destroys...the great criminals and bends in two their violent schemes like straws, in such a powerful and brilliant way that men, seeing the terror of it...submit in trembling and wonder to the power that forbids evil...."[12]

Obviously Karl Rahner spoke for many of us in saying that "A decisive, unequivocal judgment in moral questions cannot be dependent upon unanimous consent."[13] Yet many of us with John Macquarrie, are "asking whether, underlying the divergent historical phenomena and particular formulations, there are some profound ethical convictions that are held in common."[14] And many of us who now doubt that there is "a necessary connection between advances in science and human welfare"[15] are wondering with Ian Ramsey if "whatever diversification of moral principles we find in different societies, and however difficult it may be to elucidate principles suited to complex decisions in a time of rapid social change, there will nevertheless be some principles which are so stable as to be virtually sacrosanct as long as human beings remain broadly

what they now are."[16]

THE AMBIGUITIES OF HUMAN FREEDOM

We cannot disregard the wisdom of the myth of Janus, that ancient Roman God of gates and doorways for whom the first month of every year in our calendar is named. He boasted two faces: one, directed to the future; the other, to the past.

If we do, the present is on a collision course with the past and the future. The past, because we choose to ignore it; the future because "those who do not remember the past are condemned to relive it."[17]

Moses Maimonides, in the "Guide for the Perplexed", citing Alexander Aphrodisius, said that "there are three causes which prevent men from discovering the exact truth: first, arrogance and vainglory; secondly, the subtlety, depth and difficulty of any subject which is being examined; thirdly, ignorance and want of capacity to comprehend what might be comprehended." Then he added a fourth: "habit and training."[18] I would add a fifth: the desire to be first.

It has been said that "tradition is in bad odour." Still, in making that claim, Gordon Rattray Taylor admitted that "traditions are devices to simple decisions" and while pleading for "new traditions" pleaded at the same time for a "new respect for tradition itself."[19]

To whom would he entrust the implementation of these traditions and the new powers of the life sciences? A "mature and privileged group...who can be relied upon not to misuse them."[20] To whom does he turn for definitions of "mature" and "privileged"? When he concludes "The Biological Time Bomb" with the statement that the "basic answers lie for all to read in the works of wise

men. Man is the measure; knowledge, without the corrective of charity, hath some nature of venom or malignity. It is the know-how for putting these principles into effect which is lacking", the definitions are still lacking; his thought, still obscure.

Maimonides knew man better than Taylor. Let us take man's arrogance and vainglory and submit them to the test of our own life experience. Believer or unbeliever, how many of us have any god higher than Self? How many of us have not shared the feelings of Ulrich Simon that the "physical instincts put the mind on trial in two particular ways. The desire for survival, whatever happens at anyone's expense, even at the risk of betraying all, induces an immoral, clawing attitude. My neighbor becomes my enemy because he needs, like myself, air, food, drink and space. Hence I am tempted to side with hell and all its devils if only I can live. On the other hand, I long to be quit of the torment and am tempted to universalize my desire for death in a feeling of total alienation."[21] How many of us can claim that even our noblest acts and thoughts were not permeated with some self-interest? And self-deception?

Did not Philip Léon speak of and to all of us, as Reinhold Niebuhr discerned, in describing "the mechanism of deception that is too complicated to fit into the category of either pure ignorance or pure dishonesty"? He, Léon, declared: "The self-deceiver does not believe... what he says or he would not be a deceiver. He does believe what he says or he would not be deceived. He both believes and does not believe ...or he would not be self-deceived."[22] Did he not speak to the human condition in his description of collective egotism as that of individuals who "join to set up a god for whom each then

severally and tacitly identifies with himself, to swell the chorus or praise which each then severally and tacitly arrogates to himself"?[23] It is important that we hear again the words of Niebuhr in introducing those of Léon: "The mechanism of deception is too complicated to fit into the category of either pure ignorance or pure dishonesty." St. Paul said it one way: "I fail to carry out the things I want to do, and I find myself doing the very things I hate."[25] St. Augustine said it in another: "The mind commands the body, and it obeys...; the mind commands itself, and is resisted. The mind commands the hand to be moved, and such readiness is there that the mind is scarce to be distinguished from the obedience. Yet the mind is the mind, and the hand is body. The mind commands the mind to will and yet, though it be itself, it obeys not... it commands itself to will, and would not give the command unless it willed; yet (that is not) done which it commands."[25]

Unfortunately, "Few books of evolutionary or social science put these two models of man together."[26] As Langdon Gilkey has observed: "Most books of the sciences of man, in their 'scientific' sections portray man as determined by...forces that determine his behavior...and that of his group, and that make his ideals epiphenomenal at best. But in their 'prophetic' sections at the end of their books, when they discuss human destiny and the possible uses scientific knowledge can offer toward the eradication of human evil and the improvement of the human situation, these same authors tend to see man as rationally motivated by their own liberal ideals...."[26]

This brings us to the second of the causes which prevent man from discovering the exact

truth - the subtlety, depth and difficulty of any subject which is being examined. At the 1964 Study Week of the Pontificia Academia Scientiarum which was dedicated to the consideration of psychology and the neurosciences, Sir John Eccles lamented the absence of philosophers and admitted that "all sciences have a philosophical basis" and referred to their "different linguistic usages".[27] How real the problem of language is, can be readily discerned by the scientists in reading St. Augustine on will or memory:[28] or by the layman in reading the discussion of this Study Week on "determinism versus free will"[29] or memory,[30] to say nothing of the work of Gordon Rattray Taylor.[31]

In the face of the magnitude of these problems, imagery and symbols such as "biological 'engineering'; the 'manufacture' of chimeras; the 'manufacture' of man; 'hybridization' of human with other animal life to see what comes; the control of our biological 'inventory'; 'enforcing' birth control; sex for love, marriage for breeding; genetic 'tailoring'; cures 'wrought' upon or 'done to' future generations as purely passive subjects' would appear, as Paul Ramsey has declared, "logical successors to Kinsey's plumbing and electrical analogies: 'inputs' and 'outlets'."[32]

There is no scientific problem that is without some relationship to every other scientific problem. And there is no scientific problem without its implications for the humanities. Nature is one. Jean Charon is living indictment of us all when he writes of emerging from his cave and seeing landscapes never described for him by the biologist, or the psychologist, or the palaentologist, or the philosopher, or the artist or the theologian."[33] I accept his judgment upon those of us in theology. The same

judgment was made by Dietrich Bonhoeffer, over a quarter of a century ago. The Church, he wrote, "has not borne witness to the truth of God in such a manner that all pursuit of truth, all science, can perceive that it has its origins in this truth."[34] The same has been said in recent years by Mircea Eliade, Paul Ricoeur and Langdon Gilkey who contends that "many of the religious symbolic forms characteristic of ourselves and our history which secularism does not in fact understand, and so...call for religious symbolization, namely the mystery of our freedom, its proneness to waywardness, and its seeming bondage to 'fault', and the mystery of our intentions and meanings in relation to the currents of destiny."[36]

Charon calls all mono-dimensional men to multi-dimensional study and dialogue. Speaking to biologists, he urges those who are engaged in research on the problems of memory to begin by asking physicists...about the concepts of space and time. "Now", he observes, "this scarcely ever happens. In the first place...the biologist is nearly always first and foremost a phenomenonologist." Furthermore, "he removes the living material from its space and time environment." For Charon, "it is not possible to argue from this concept, purely in terms of corpuscular or mechanistic language." As he sees it,"the biologists need to adopt the notion of a field in order to be in a position to make effective use of the physicist's space-time in <u>their</u> language.... In short, biology needs to make the same advance as that which took place in physics about the middle of the nineteenth century when the language of Ampére and Faraday was superceded by the language of Maxwell, the latter being based upon the idea of a field, that is to say, upon the notion of a

structure that might be characteristic of space-time, but not matter."[37] Among Charon's singular contributions are his own concepts of "archetypal blockage"[38] and "symbolic imbalance"[39] which he finds responsible for the "disappearance of the religious sense" and "the growth of psychosomatic disturbances." The problems are many. The options for the interpretation of any problem are as many if not more. Happily, men in the natural sciences are reaching out toward those in the humanities and men in the Church toward those in science. The options of interpretation discerned by Charon are as clearly visible to Bishop Ramsey. Turning to the area of Charon's immediate interest, he says: The axioms of mathematics are only options and by now it is notorious that Euclid does not give us the only possible option - what of Lobatchewsky, Bolyai, Riemann and the rest?"[40] How essential a sense of humility is to the solution of man's multi-dimensional problems becomes transparently clear in Paul Ramsey's critique of the mono-dimensional thoughts of Joshua Lederberg who, Ramsey insists, "does not want only scientists to make public policy, (but) wants only a scientific judgment to be made."[41]

This brings us to the third cause which prevents us from discovering exact truth: ignorance and want of capacity to comprehend what might be comprehended. While an undergraduate in college, a friend of mine often said: "For every smart man, there is one smarter." I have long pondered those words. They not alone underscore our "Fachmann" approach to education; and our claim to knowledge as knowledge of a special field of learning but they point to the attrition of wisdom that accompanies the growth of knowledge and man's Procrustean attempt to

solve the most complex problems with the most simplistic devices. Gordon Rattray Taylor, in discussing the future of genetic 'engineering' and realizing the mistakes that are bound to occur, writes: "The necessity of destroying the defective embryos, which constitute abortion under present law in many countries, will no doubt arouse resistance. Those countries which do not consider destruction of the embryo to be abortion until after the fifth month of pregnancy, or some other stated period, will then be at an advantage."[42]

Jesse Dukeminier, Jr., in his paper on "Supplying Organs for Transplantation" discusses the possibility of using clones (an exact genetic copy of a human being) for transplantation. Then, there would be no threat of rejection, no need of immuno-suppressive therapy. Of course, he sees that "the issue would inevitably arise whether clones are people and thus entitled to the respect due a human being and to equal protection of the law." His answer: "Dr. Roderic Gorney has suggested that this difficulty might be circumvented by keeping the clone in unconscious storage so that it never develops a mind and human personality."[43]

Joshua Lederberg raises a few more questions. Mentioning the "futility of negative-eugenics programs"; admitting that "public advertisement and availability of 'superior germ plasm' (sperm banks)...would probably run very differently from sponsor's hopes"; stating openly "What to do with the mishaps (in scientific experimentation) needs to be answered before we can undertake these risks in the fabrication of humans"; conceding that "medico-technological aspects of human performance are more predictable than the socio-political", he finds that "We are on the shakiest ground trying to sort out the

genetic basis of such social diseases as crime and deliquency"; and wonders "how inadequate the scientific ground work is to determine how far the statistics of female performance in industrial society are biologically versus socioculturally determined". Assuming "that genetic identity confers neurological similarity, and this eases communication", he then - as countless men throughout the ages - raises the ultimate question, "Who is human?". Asking "how is it possible for man to demarcate himself from his isolated or scrambled tissues and organs on one side, and from experimental karyotypic hybrids on another?", he suggests that "the legal privileges of humanity will remain with objects that look enough like men to grip their consciences, and whose nurture does not cost too much" but commends "a more rational criterion of human identity (which) might be the potential for communication within the species, which is the foundation on which the unique glory of man is built".[44] In this one article, he writes with precision in scientific matters; with imprecision in others. "Consciences", "cost", "rational" and "potential" are left undefined.

It would be difficult in these times to be ignorant of the differences which exist in the communities of science,[45,46] law,[47] and religion[48] but it would be symptomatic of that blindness that glories in being blind[49] to remain ignorant of the implications of these divisions for every man, woman and child. Joseph Fletcher, for example, is still arguing the beginnings of life and still insisting that "it is difficult to check off any specific point on the gestational continuum as the start of a human being"[50] that which would permit the use of 'fetal material' for experimentation and transplantation *in vivo* and *in vitro* and provide grounds for its

destruction as 'non-human' if his argument were to be accepted. And this in face of the California Medical Association's admission of "the scientific fact, which everyone really knows, that human life begins at conception and is continuous whether intra- or extra-uterine until death" while insisting that "No other discipline (than medicine) has the knowledge of human nature, human behavior, health and disease and of what is involved in physical and mental well-being".[51] If this argument were accepted, it would subsume Fletcher's discipline and all other disciplines into the mono-dimensional discipline of the life sciences.

To subscribe to the theory that one cannot define the beginnings of human life is to overlook the simple truth that "not to define is to define" and to open the door to the increasing destruction of life, the gradation of each individual's claim to life and the denigration of life itself. And "community acquiescence or indifference"[52] to the potential for good or evil inherent in these discussions, uncomprehended by the average layman save for those portions couched in the most utopian or apocalyptic popular terms, should be the first concern of those who know what violence was done man's political, social, economic and ethical systems with the development of atomic energy and anticipate no less - and fear an even greater - rupture in the fabric of world society with the application of our knowledge of genetics.[53]

The public has not only the right to know, the public has the duty to inform itself. For while "Reason is the tool of desire"; "It is the instrument by which we effect that which we are previously resolved to accomplish.":[54] while "...man, proud man...like an angry ape,

Plays such fantastic tricks before high heaven
As make the angels weep.",[55]

there is at least some hope that his capacity for self deception will be reduced by multi-dimensional popular discussion by those of different disciplines and different points of view.[56]

In all fairness to Lederberg, he sees that "there is no gene that can ensure the development of a child's brain without reference to tender care and inspired teaching".[57] Still, if the truth of love is not to be turned against the love of truth,[58] I must say with Martin Golding, "If someone finds it difficult to think of having an obligation towards his unborn child, then he should find it difficult to think of having an obligation toward a community of humans (humanoids?) fifty generations hence". And with him, "I must confess to finding it odd when the same people who put biological engineering for the future on ethical grounds also defend abortion of a foetus on the ground that we have no obligation in respect of an unborn child".[59]

This brings us to the fourth cause which prevents us from discovering exact truth: habit and training. The scientist is anxious to get on with his experiment: the philosopher and theologian are, for the same reason, patient and more cautious.

Lederberg, the scientist, in viewing the future prospects of biological 'engineering', observes that the "introverted and potentially narrow-minded advantage of a clonish group may be the chief threat to a pluralistically dedicated species".[60] Rahner, the theologian, sees "partial genetic manipulation" producing "two 'new' races...the technically manipulated 'well bred, retort man' with an inevitably special status in society and the 'average' not selected

commonplace man, who originates in the old fashioned way. What new social tensions would arise and this in a time when racial discrimination and conflict are assiduously being overcome...! Or does one believe that this group of retort men who from birth have given evidence of an essentially higher intelligence quotient would renounce this special position in society and would not attempt to have the remaining 'mass humanity' (without benefit of breeding book) obey them? Would the remaining members of mankind who would be at least as intelligent, revolutionary and powerful as we willingly submit to the leadership claims of the breeding book selected retort man?...The production of such unforeseen and, in their consequences, unforeseeable material for conflict must...be termed immoral since this is directed against man and mankind".[61] Is it possible for the scientist, philosopher and theologian to converse and to agree? Wolfhart Pannenberg believes that in his country, at least in the late fifties and early sixties, they "found related insights and to some extent even a common language in the question about man".[62]

To say the least, the exchange among Europeans has been marked by a candor which indicates an awareness of history. It has been as refreshing as it has been unique. In his comments on the Ciba Foundation Symposium, "Man and His Future", Walter Heitler observed that "In the entire report of the conference that concerned itself principally with human genesis, I did not find the word 'love' one single time". Later, he added: "In these suggestions for betterment, the human element is eliminated. With thoroughgoing logic, man is described as a molecular system".[63] Wilhelm Kütemeyer, in criticizing some of his geneticist-colleagues, said of their restlessness

to apply what they have learned, "The unforeseeable is not reckoned with. The urgent is not attended to. The inevitable is not existent."[64] Friedrich Wagner, while not a scientist, found himself in agreement with his colleagues in science. Of the geneticists he said, "(they) have no concept of man and no standard of value which bind them nor a methodology or goal in research which they hold in common."[65] Yet it is Bishop Ramsey - with his irenic spirit - whose words on the value of life, whether that of the individual or the species, may well prove the most penetrating. He raises the question of a need for survival and a need for law. "If survival is to be basic to a new Natural Law, there must be a moral necessity about survival, granted that men and the world and society are what they are today."[66] "...it is in recognizing a dominant moral claim about 'survival' that we recognize ourselves as distinctively persons... traditionally the recognition of Natural Law has been supposed to be somewhat definitive of human personality. For this is in effect none other than the old point that we become persons in discovering a moral obligation."[67] "...such a basic moral insight gives rise to 'natural necessities' when we judge that certain rules accord with, or match with what the idea of survival portrays as obligatory. These are the more positive 'natural necessities'. But there are also negative necessities, e.g. the prohibition of certain kinds of killing and violence."[68]

No matter what type of society man may devise, there can be no law without order nor order without law but they are meaningless without justice. In turning from insistence upon our rights to acceptance of our duties and from the self-alienation of self-indulgence to the self-

discipline, we may again find the root cause for our use of the words - "Conscience" and "Moral Law" - in that " we live, think and value...."[69] In truth - Sum, ergo cogito, ergo aestimo.

The last of those causes which prevent men from discovering the exact truth is the desire to be first or the first by whom the new is tried. This is not to deplore inquisitiveness, to block research or to denigrate man's restless creativity. This is to counsel patients in applying the insights of our own discoveries lest we naively distill evil from good, despair from hope, disaster from our utopian dreams and saddle future generations with the irreversible consequences of the precipitate, ill considered use of our own newly won powers. The sobering thoughts of a Planck, Hahn, Einstein and Oppenheimer have already found their parallels to a degree in the experiences of Christiaan Barnard,[70] Denton Cooley[71] and Adrian Kantrowitz;[72] and in the public statements of James D. Watson.[74]

THE AMBIGUITIES OF LIFE

No one among us has failed to experience the contingency of the finite. Gilkey recounts the story of his own experience in moving terms. Describing one of his once-upon-a-time favorite television programs sponsored by an insurance company, he tells of the mellifluous voice of the announcer asking: "Do you wish to guarantee the health and happiness of (your) loved ones against every contingency? Then buy our packaged policy, and...be assured against every mishap." Then he recounts the words of the newscaster who, for a half an hour, told his audience "just how serious is the present situation in Cuba!" At midpoint and at the end of the program, there was again that mellifluous voice and that selfsame

commercial, "Do you wish to guarantee...your loved ones against all possible contingencies?" All that Gilkey could envision at program's end was the pathetic figure of a man "standing alone in the middle of a bombed-out, suburban lane, waving that package policy".[74] No one among us has failed to experience the relativity of all things to one another in the passage of time. Those of my generation have witnessed the "Götterdämmerung" of Adolph Hitler, the rise and fall of Stalin, the beginning and end of de-Stalinization and the 'unpublicized' death of and infrequently visited grave of Nikita Khruschev. Yet is it not strange that "...science which has, more than anything else, taught man his contingency and relativity, and seriously to consider himself the potential master of his own fate."?[75]

No one among us has failed to experience the flow of time and his own temporality and transcience. For us, as for St. Augustine, "these... days 'are' not; they go almost before they come; and since they came, they cannot stay; they swallow themselves, follow themselves and do not stop themselves. Nothing of the past lets itself be recalled; what is future is anticipated, as something transitory; yet one does not possess it so long as it did not come; one does not detain it since it did come."[76]

The ancient Israelite; Plato and Aristotle; St. Augustine, Moses Maimonides and St. Thomas Aquinas; to say nothing of their more recent followers knew these concepts. But for them - unlike modern man - the contingent implied the unconditioned; relativity implied the absolute; and temporality implied the eternal. Modern man, as Gilkey so clearly demonstrates, asserts contingency and temporality "about reality as a <u>whole</u>".[77] Indeed, "All is becoming, all is changing, all is in passage..., and so all causes

and all effects come and go - and all is mortal - and nothing else is real. There is in direct experience nothing else besides creatures 'which never really are' - and death as perishing claims all creatures".[78]

The implications of this thought for biology are incalculable. As Paul Ramsey sees it, "Our culture is already prepared for technocratizing the bodily life into collections of parts in which consciousness somehow has residence for a time, and for calling by the name of 'the direction of mankind toward God' what can better and exhaustively be described in secular terms as the onward thrust of technological progress."[79]

Admittedly, in "this dimension of experience, which concerns the dim horizon of ultimacy within which we live, we may make negative as well as positive statements; we may discover and thematize only a void and affirm that no answer arises here at all; or we may find an answer and develop (a) range of language on its basis. In either case, we are using what we call 'religious' discourse, for we are discoursing either in negative or in positive terms, either in terms of mere questions or of experienced answers, about the ultimate and unconditioned context of our life".[80] With Ian Ramsey, "I do not know what 'purely subjective' experience is - all experience is of something."[81] With Gilkey, I find that "...all thought is 'theory laden'."[82] And it is his emphasis upon the interrelationship of being, thought and value, and his "hermeneutic of secular experience"[83] that, I believe, constitute his most significant contribution to the present discussion. "Our experience," he contends, "touches these depths, this region of ultimacy, at each crucial moment of our careers, and a sense of their significance is always there, seen or felt, so to speak, out of the corner of

the eye." Therefore, it is "on our relations to and decisions concerning this realm, (that) everything in our life that is of importance or value depends. For this reason, this realm has not only the character of ultimacy, but also of the sacred: it is the ground not only of being, but of all value."[84] As Paul Tillich said, "We are aware of the power of being through the experience of the shock of non-being"[85] and "the question of the ultimate is a question about our own being"; or, as Tillich said, "In this region we do not have a question, we are the question."[86]

We may equate ultimacy with the Ground of Being[87] and man's commitment to it as his ultimate concern.[88] We may talk of God. Or we may talk of the Void or the Absurd.

Still, the link between being and value remains and the question of morality and law continues to haunt us. Therefore, with John Macquarrie, I believe that "one may think of Albert Camus, who visualized man's position to be as hopeless and absurd as that of the mythical Sisyphus.... Yet Camus saw this godless situation as a challenge to greater moral effort".[89] One may argue with Ulrich Simon that the "doctrine of the divine superman died at Auschwitz"[90] or with Macquarrie that it did not and "there may have to be many more occasions of atonement before it dies".[92]

But surely few can argue with Simon's thesis that it "is an affront to reason and experience to shelve the problem of love by playing a false trump-card, such as 'Love God - or man - and do what you like'. Even the support of a few Bibical texts cannot alter the fact that we cannot love as we would and that our inability to love is text-book stuff in every clinical log-book. The Auschwitz shadow pursues us everywhere in the obsessional blindness of eyes and deafness of

ears which seek release in destruction, and not in love." He insists that "We...argue in a circle if we commend love as the main-spring of action, when love - even if well-defined as an attitude of the will - is yet to be won by healing."[92] And he views "the legacy of Auschwitz (as) a constant warning against relativity and tolerant judgments in matters of human conduct."[93] In this condemnation of situation ethics, he goes beyond Father Bernard Häring, who would put "his finger on the essential weakness of (Joseph) Fletcher's ethic when he says that "Fletcher's concept of love is structureless".[94]

In "The Cup of Trembling", Erich Friedhoffer, who portrays the real-life Dietrich Bonhoeffer, underscores Simon's view. While being cross-examined by the Gestapo, Friedhoffer answers every question with a patient, well considered reply. As his interrogators leave him, they taunt him with their advice that he take care of the things of the next world and leave to them the affairs of this world. With this, he turns in anger upon them and shouts, "They told you there was no heaven but did they tell you there was no hell?"[95] As a Christian, I can share Simon's cry of anguish so similar to that of Rabbi Richard L. Rubenstein and yet so different, for - after Auschwitz - the rabbi can no longer accept a God who is Lord of history or enjoys any special relation to the people of Israel[97] while Simon can still hope and believe. I think we must hear these voices and that of Emil Fackenheim. He finds "all categories which do justice to but relative commitments" too puny; "all past categories...inadequate, even when they do justice to absolute commitments, if only because religious categories exclude the secular, and secularist categories, the religious. Nothing less will do than to say that a <u>commanding Voice</u>

speaks from Auschwitz.... Transcendence is found at Auschwitz in the form of absolute Command." Then, he asks, "What does the Voice at Auschwitz command?" First, he answers, "We are commanded to survive as Jews." Second, "We are commanded to remember...the martyrs of the holocaust." Third, "We are forbidden to deny or despair of God...." Finally, "We are forbidden to despair of the world...lest we help make it a meaningless place in which God is dead or irrelevant and everything is permitted."[97]

The voice of the Wholly Other may be heard again in the land. The famine and drought of which which Amos spoke may be broken.[98]

With Karl Rahner, I must confess that "It is easier to let oneself fall into one's own emptiness than into the abyss of the Blessed Mystery. But it is not more courageous or truer."[99] With Walter Leibrecht, I believe, as Hamann of whom he writes that "Knowledge of self and knowledge of the world are inseparable":[100] and only "action which jointly springs from all of man's faculties, which is consequently the action of the whole man, is action conformable to reality, to all reality."[101] With theodosius Dibzhansky, I believe that "What is established as a biological adaptation is the ability to 'ethicize', not the nature or the contents of the ethical tenents."[102]

Finally, with Ian Ramsey, I believe that once "the possibility of a theological link for the language of science has been logically admitted, both theology and science in practice will be largely concerned to develop their implications in terms of models, and this will commit both disciplines to personal humility and to tentative conclusions."[103]

In that spirit, I would call upon all who hear my voice or read my words to join in the multi-

disciplinary, multi-dimensional discussions so necessary to achievement of some viable answer for our time to the great questions raised anew by the Communist philosopher, Ernst Bloch: "Who are we? Whence do we come? Where are we going? What do we anticipate? What awaits us?".[104] The stakes are high; the issue - nothing less than the future of man. And while science has every right and duty to emphasize man's immanence in nature, as Darwin has done, the theologian, philosopher and humanist have the duty and should exercise the right to emphasize man's transcendence over nature and the good and evil which that trancendence can achieve as the history of our times so clearly proves.

You may think Franz Vonessen's judgment harsh. He claims that "science has ceased to serve man; instead man for his part has comforted himself in the compulsory service of knowledge. He reveres this Moloch into whose jaws he pours the entire riches of the earth, to whom, accompanied by the applause of the majority, even the most Christian representatives, he gives year after year billions of dollars, and to whom he is now ready to sacrifice himself on the sublime road of 'human' genetic suicide."[105] And I may think Ulrich Simon's judgment harsh when he states that "the failure of theology has been and remains at the root of our enslavement. Its abstract terminology could not prevent the great disaster (the holocaust)."[106]

But I think we must ask if they are not right: and if we have failed our fellowmen and ourselves in not devising a language which allows us to communicate with them and one another. The "prospect of a genetic twilight" is as nothing compared to the "certainty of a moral twilight" if we do not.[107]

As Romano Guardini has pointed out, the ancient

world sought to attune itself to the inner harmony of a divinely established universe whose principal earthly steward was the man of excellence. The medieval period sought to bring its existence into accord with a transcendent authority and holy power who dwelled in the highest heaven. The modern age ought to gain power over nature through the application of rational knowledge and precise technics.[108]

Now that the modern age has ended[109] and we live in an epoch to which we have yet to give a name, what does this mean for the future of man? His power increases. Power begins to assume a form of its own. We are only now becoming conscious of its character and its dangers.[110] Now we can see that the central problem of the yet-to-be-named age in which we live is the challenge posed us to find the power within us to restrain, to temper and then to master that power which rages uncontrolledly without us - to which we gave birth.

The principal ethical issue raised by advances in genetics comes with two questions: "Can we control ourselves?" and "Can we control the power we have created?". On our answers rests the penultimate if not the ultimate future of man and we had best turn to the ultimate if we would serve the penultimate and man.[111]

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SUBJECT INDEX

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GENETICS, ENVIRONMENT, AND BEHAVIOR

IMPLICATIONS FOR EDUCATIONAL POLICY

Edited by LEE EHRMAN
GILBERT S. OMENN
ERNST W. CASPARI

1972, 344 pp.

This book presents the fruits of a conference—one of a series organized by the Committee on Basic Research in Education on social, political and biological aspects of educational policy. Its subject is the interrelationship between genetic and environmental factors in the development and maintenance of behavior. Leading researchers in many fields—including animal behavior, ethology, population genetics, psychiatry, sociology, behavior genetics, and others—have contributed papers which not only shed light on specific problems in various specialities, but also combine to provide an integrated view of the subject as a whole. Topics discussed include:

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- Relationships between behavior and evolution;
- Gene-environment interaction in determining behavior;
- Methodology in the analysis of human behavior genetics.

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