The genetics of migrant and isolate populations : proceedings of a Conference on Human Population Genetics in Israel, held at the Hebrew University, Jerusalem / edited by Elisabeth Goldschmidt.

The Genetics of Migrant and Isolate Populations

The Genetics

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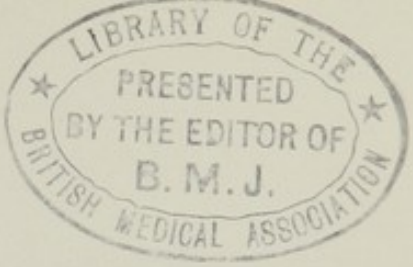
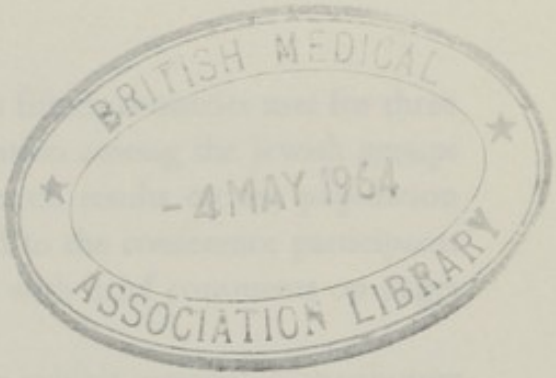


# of Migrant and Isolate Populations



PROCEEDINGS OF A
CONFERENCE ON
HUMAN POPULATION
GENETICS IN ISRAEL
HELD AT THE HEBREW
UNIVERSITY, JERUSALEM

EDITED BY
ELISABETH GOLDSCHMIDT
DEPARTMENT OF ZOOLOGY
HEBREW UNIVERSITY

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PREFACE

In September 1961 a group of geneticists from fifteen countries met for three days in Jerusalem to discuss the genetic differentiation among the Jewish groups of Israel. A broad selection of the available research results on the population genetics of the Jewish communities was presented to the conference participants in the form of a pictorial exhibit, which appears with brief comments on pages 251 *ff.* of this volume.

The five conference sessions were based on the exhibit material. Contributors who did not refer explicitly to the problems of the short-range evolution of the Jewish communities described their approach to related aspects of differentiation in other population groups. All of these discussions illuminated rather relentlessly the gaps in the existing information on the Jewish groups and their micro-evolution. Thus, although these Proceedings may contain more data on the genetics of Jewish populations than have ever been assembled, they represent a notebook for future workers in this field rather than a compendium on this subject.

In the early stages of its activities the organizing committee of the conference was fortunate in obtaining the wholehearted response of the Hebrew University, the warm support of Dr. S. Syman, Director General, Ministry of Health, and the unfailing advice of Dr. Thomas D. Dublin, Chief, Epidemiology and Biometry Branch, National Institute of Arthritis and Metabolic Diseases. The Office of International Research, National Institutes of Health, made an important contribution by sending a group of leading United States geneticists to the meeting.

The success of the conference was due in large measure to the planning by the secretary, Dr. Raphael Falk, and to the devoted efforts of the staff and research students of the Department of Zoology at the Hebrew University.

The editor expresses her gratitude to the Association for the Aid of Crippled Children, New York, for its generous support of this publication.

Dr. R. Falk and Dr. H. M. Slatis gave valuable advice on editorial procedure. The original exhibit charts were designed by Mr. E. Lehman and Mr. E. Preis. Mrs. I. Mizrahi and Mrs. Y. Preis prepared an excellent typescript.

The cooperation of the contributors to this volume is gratefully acknowledged.

ELISABETH GOLDSCHMIDT
Jerusalem, December 1962

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CONTENTS

SESSION 2 A. C. ALLISON, *Chairman*

ADAPTIVE VALUES OF ERYTHROCYTE DEFECTS AND THEIR CHANGE WITH ENVIRONMENTAL CONDITIONS

SESSION 3 A. G. STEINBERG, *Chairman*

THE INFLUENCE OF ENVIRONMENTAL CHANGES AND OF ETHNIC FACTORS ON THE INCIDENCE OF SOME COMMON DISEASES AND MALFORMATIONS

SESSION 4 J. V. NEEL, *Chairman*

GENETIC STUDIES IN ISOLATES

SESSION 5 C. STERN, *Chairman*

THE CONCENTRATION OF RARE GENES IN THE PAST AND IN MODERN TIMES

EXHIBIT SECTION

THE GENETICS OF ISRAEL'S POPULATIONS

BIOCHEMICAL DISORDERS AND RARE DEFECTS

ENVIRONMENTAL EFFECT OR ETHNIC DIFFERENCE?

MATING SYSTEMS

CH. SHEBA, *Chairman*

INTRODUCTORY SESSION

CH. SHEBA

Your Excellency the Minister of Education and Culture, the Rector of the Hebrew University, Prof. Haldane, fellow geneticists from abroad and from Israel, ladies and gentlemen:

I greatly appreciate the honor conferred upon me by the members of the Organizing Committee and of the Program Committee, who asked me to deliver the welcoming address. It had been my dream for some time to see geneticists and hematologists from Mediterranean countries and from more remote areas assembled here in Jerusalem for a conference on environmental and inherited factors responsible for Mediterranean diseases. It was a fortunate coincidence that Dr. Motulsky, of Seattle, Washington, independently suggested this conference and that, jointly, we found response.

We hope that this conference will fulfill a triple purpose. First, it may strengthen the bonds of cooperation that already exist between the various groups of geneticists around the Mediterranean, and it may lead to the creation of a Mediterranean club for human genetics. But the willing response to our invitations on the part of eminent scientists from other areas proves to us that the present structure of Israel's populations may indeed attract the interest of human geneticists in general. We feel fortunate that in planning research on our rapidly changing communities we may enjoy the advice of distinguished authorities gathered here today. Finally, we trust that the medical profession will be stimulated by this conference to embrace genetics and to assign it to its rightful place in both medical and veterinary education and practice.

I welcome all of you most sincerely and wish to thank you for the trouble you have taken to come such a long way to join us. It is my privilege to acknowledge gratefully the support rendered this conference by the Association for the Aid of Crippled Children, of New York, which is represented here tonight by Dr. C. A. Swinyard. The Office of International Research of the National Institutes of Health, represented here by Dr. R. E. Knutti, assisted our conference by delegating a number of prominent United States geneticists to attend. Our thanks go also, last not least, to the various ministries of our government, including the Prime Minister's Office, and to the Hebrew University, our most generous host.

I should like to call on his Excellency the Minister of Education and Culture, Mr. Abba Eban.

MR. ABBA EBAN

I thank you, Mr. Chairman, for investing me with this Legion of Honor [*laughter*]. The government and the people of Israel, for whom I speak tonight, attend your conference with deep emotion and respect. I was happy to be able to

cooperate with Dr. Goldschmidt and Dr. Sachs in the processes which brought this conference to pass.

Ladies and gentlemen, we stand here upon mountains, the mountains of Jerusalem, whence the echoes of great voices have been heard by countless generations of mankind. If I were asked to summarize the intellectual history of the Hebrew people, which had its birth and has now had its renewal here, I would say that the genius of the Hebrew mind since its earliest days has been revealed in a constant obsession with the spectacle of life. In our conception the greatest theme which men can study is man. This would be true in any age, but it is a truth of special insight in these agonizing times when man's evolution has brought him to a point of utmost peril in his destiny. Standing in the proud conquest of his external domain, he finds his victory annulled by a failure to master his inner realm. And thus, in conditions uniquely favorable to the unification of mankind, he finds himself lacking in a sense of inward or outward order, living a fragmented life in a broken and disunited world. Surely science has some message in this confusion of our times. The hallmarks of the scientific mind are its critical temper, its constructive rationality, its intellectual humility. Science, in the words of one of its greatest contemporary exponents, is the effort of the human mind to enlighten itself by evidence; not only does critical science not claim definitive finality for its conclusions; it understands why such claims of finality may not be made.

Wherever men of science from different lands come together, they must be acutely aware of their duty toward the total human situation. There are austere theories of purity in science which would insulate the research worker from all subjective calculations, which would confine him to his library and laboratory, giving no thought to the universal effects of his insight and conclusions. This view is becoming increasingly discredited. The scientist is not only a physical part of the universe which he investigates; he is also a responsible member of the human society which taught him his skills, which gave him the opportunity to express his inner self, which accorded him the position of respect which he rightly maintains. And thus the leading scientific thinkers of our time are becoming increasingly conscious of the fallacy of a scientific rationalism uninhibited by moral and ethical restraints.

The subject of your deliberations brings you to a point of intersection between the natural sciences and the science of man. Here, in the exhibit and in the special themes of your study, you will find the Jewish people under special scrutiny. We believe that, through circumstances of its history, this Jewish people offers a microcosm of human life and experience. Whatever has happened to the human species has in some measure or degree happened to us.

We hope, then, that the conditions of the place will help you to make further advances in your investigations. We believe that the present holds within itself the complete sum of human existence, backwards and forwards, the whole amplitude of time which is eternity.

You have a lofty theme for study. I am confident that you will illuminate it by the cooperative efforts of your minds and hearts.

SHEBA: Thank you, Your Excellency. I should like to call now on the Rector of the Hebrew University, Prof. Racah.

PROF. G. RACAH

Mr. Chairman, Your Excellency, Prof. Haldane: I am very happy to be here tonight and to extend the greetings of the Hebrew University to the Conference on Human Population Genetics in Israel. I extend a warm welcome to the distinguished scientists who will be participating, and especially to the many who have come here from abroad. I want particularly to thank Prof. Haldane for having accepted our invitation to act as President of the Conference. I am sure that Prof. Haldane's presence is a splendid augury of what we may expect from it, of the high level on which its discussions will be conducted, and of the stimulus it will give to the work being done by geneticists in this country and abroad.

To us of the Hebrew University, it is a particular source of pleasure that the conference is being held on our campus, and I hope I am not wrong in thinking that the choice of venue was dictated in some measure by the high standards which studies in genetics have attained in our Faculty of Science. But, of course, there were other considerations in this choice. Israel, with its diverse populations, drawn from so many parts of the world and so many different environments, presents a unique laboratory for the geneticist. I have no doubt that the knowledge and experience gained here will be of no little benefit to the visitors from abroad. Similarly, the knowledge and experience gained by the geneticists in other countries, working among different populations, will be no less important to our scientists in this country. The exchange of information and ideas will, in fact, be one of the greatest achievements of this conference.

SHEBA: Thank you very much, Prof. Racah. I should like to call on Dr. Goldschmidt to address the gathering, which, as I said, is in great part her responsibility and her success.

DR. E. GOLDSCHMIDT

Mr. Chairman, Mr. Eban, Prof. Racah, ladies and gentlemen: It is a great pleasure to the members of the Organizing Committee to see our honored guests from many countries and from Israel here with us tonight. We are grateful to all of you who have been willing to give of your time and of your advice to our group

of Israeli workers, and to sit down with us for three quiet days in order to discuss the problems of human population genetics which may be studied with advantage here at the present moment.

Dr. Sheba, our enthusiastic Vice-President, Dr. Falk, our untiring Secretary, and all the members of the Program Committee will agree with me that for us this is a moment not only of great happiness but also of enormous relief. At long last we are able to pass over the responsibility for these meetings to our five distinguished chairmen, and the scientific leadership of the whole conference to Prof. J. B. S. Haldane, our honored President [*applause*].

We may consider ourselves fortunate indeed that Prof. Haldane has accepted the presidency of this conference on short-range evolution in human populations. Human population genetics is one of the several fields in which you cannot move without encountering the approaches and analyses of Prof. Haldane at every step. Our concepts of breeding systems and selection, of mutation rates and equilibrium, of dominance and its evolution, have been shaped to a very large extent by him. He has designed the tools which we are applying today, and he has perfected and sharpened them in the incessant work of many decades.

Some of Prof. Haldane's ingenious proposals, such as that concerning incomplete sex-linkage in man, have kept us busy with discussions for long years. His mere casual suggestions, such as that concerning the adaptive value of thalassemia in malarious areas, have set off a chain of fruitful investigations and debates.

For all these reasons, it is an enormous privilege for us to be allowed to carry on this conference in his presence and under his guidance.

SHEBA: May I call now on our honored guest, the President of the Conference, Prof. J. B. S. Haldane.

PROF. J. B. S. HALDANE

Mr. Chairman, Mr. Rector, Your Excellency, Dr. Goldschmidt: My first task is to thank you all for the trouble which you have taken in organizing this congress and for the hospitality, which we have already tasted of to a considerable extent.

We are meeting here in the city of David. There are two types of heroes, the not very intelligent hero like Samson and the intelligent hero like David. Both are admirably described in your ancient liturgy. For 3000 years the story of David and Goliath has inspired heroism. The heroes have often died as David would have died had his first stone not killed the giant. He was intelligent enough to realize that. He was also intelligent enough to realize that if he were killed, somebody else would come along with another stone. I know something about this type of heroism, as I was myself concerned with the miniature submarines, the crews of one of which destroyed the German battleship Tirpitz in 1944. I know that type

of heroism which attacks something considerably larger than itself and which doesn't say, "when I come back" but says, "if I come back."

I think that nothing which I have seen in Israel moved my own emotions more than the brook in the Valley of Elah from which David took the stone. Unfortunately, when we crossed this brook I couldn't stop the bus, but I will ask you, Sir, for one present from Israel: a little stone from that brook. I am getting old. Goliath is always telling me that he is a decent fellow enough, and with a little statesmanlike compromise on my part we might get on very well. I want that stone, Sir, to renew my youth.

Many kings have been heroes, but David was also a poet. I don't know how great a poet he was because, unfortunately, I cannot read Hebrew, but it can be argued that he was the most important poet that ever lived. Today millions of people, every hour, are singing his Psalms, mostly extremely badly mistranslated, and all later Jewish, Christian, and Islamic poets have been influenced by him and by those later Jewish poets who were proud to write under his name.

Now, as a biologist let me tell you what strikes me most, as most original and surprising in the poetry of the Psalms. Other ancient poets have glorified religion and war. It was left for the Psalmists to stress in a quite unique manner man's relations with the plants. I will only quote a few of many passages:

"Thy wife shall be as a fruitful vine upon the walls of thine house; thy children as the olive branches round about thy table."

Not only were individual humans identified with plants but in one of the latest of all Psalms Israel as a whole was so identified. "Thou hast brought a vine out of Egypt . . ." I needn't go on; you all know how it goes. But I sometimes wonder whether that identification, both of individuals and of the whole people, with plants does not explain to some extent the extraordinary enthusiasm not only for agriculture but for forestry which one sees in Israel today. I am quite aware that there are other sources for that enthusiasm. When I went to the Negev, I immediately thought of Isaiah's prophecy: "The wilderness and the solitary place shall be glad for them and the desert shall rejoice and blossom as a rose. It shall blossom abundantly and rejoice with joy and singing." That seems to me, as a mere biologist, one of the most remarkable features of the literature of this country and one which, I believe, may be responsible for the remarkable blossoming of biology in Israel today.

But, Sir, I am not clear why you asked me. I am an ancient monument and, of course, you, Sir [referring to Dr. Aharoni] are very interested in ancient monuments, even when they have been the sources of false opinion, idolatry, and so on. I hope that, although I am an ancient monument, people will not hesitate to state that my opinions are idolatries which should be destroyed like the Golden Calf. If I can be useful in that respect, then it is worth while having me as president, but I hope that no one will be more polite to me than Moses was to the Golden Calf.

There is one reason, however, why it is desirable that at least India should have some representative. There are countries in Africa where endemic malaria still exists and in which it is possible to study the function of the abnormal hemoglobins. But there are certain difficulties there. The method is rarely experimental. I couldn't visit Mount Carmel without thinking of the perfect example of a controlled experiment—Elijah's bonfire and the bonfires of the priests of Baal acting as a control. The experiment succeeded; the control was negative. And we can do that sort of thing, to some extent, with the abnormal hemoglobin and the *falciparum* malaria. But only some of the African populations possessing abnormal hemoglobins also have appreciable quantities of the genetic abnormality in an enzyme which leads to favism, on the one hand, and gives protection against malaria on the other. I think we have some of that in India, and I regret to say we have not quite extinguished malaria, but I hope we shall have in another three or four years. And I very greatly hope that we can arrange at this conference for someone to come over and study one or two of the few areas in India where various types of malaria are still virulent. When that is done, perhaps the function of India in this club will have stopped, because we have made a very small contribution, indeed, to Israel, mainly from Bombay and from Cochin, and perhaps that would not justify our full membership.

Well, I have talked quite enough and I only, before I sit down again, want to thank all concerned here for the work which they have done in connection with this conference, particularly Dr. Goldschmidt and Dr. Falk, and for the hospitality which has been showered upon us. I at least will do my best to be of some use in the few days which remain.

SHEBA: Thank you, Prof. Haldane, for your very warm words. I now call on Dr. A. G. Motulsky, who has been for years a source of encouragement to us, directly and indirectly, before he became the moving spirit of this conference.

DR. A. G. MOTULSKY

Dr. Sheba, Prof. Haldane, Prof. Racah, Dr. Goldschmidt: Let me explain in a few words why I thought that this conference should be held here. For the past few years I have followed with great interest the many publications that have come from Israel on genetic traits and genetic diseases in various Israeli populations and which are in line with the recent biochemical and serological advances in population studies.

Now actual field work with populations is difficult in many instances, because of scanty medical and historical records, because of poor medical care, unstable political systems, or a scarcity of interested local workers. None of these difficulties exists in this country. As Prof. Racah has pointed out, Israel is a perfect laboratory

for the study of human populations. We have here an accessible population whose history is well known. There is a fairly uniform medical standard. There are many interested and highly talented local research workers in all the branches and subspecialties required in actual field work.

At the same time, there is a tremendous official encouragement of scientific work. And, last but not least, we have here an array of well-defined populations of different origins, some of which still exist as isolates. In this sense Israel is a population geneticist's dream. Among the many promising research approaches, I might mention the study of genetic drift, of isolates and inbreeding, and also of outbreeding and intercommunity marriage. Mutation studies have to be based on good vital statistics registers. These should be available in this well-defined population of some 2 million. Jewish migrations have been described, interbreeding with other populations has occurred, and their results may be analyzed and possibly distinguished from those of selective forces. Studies of geographic pathology, of genetic epidemiology, of environmental vs. genetic influences, can also be carried out with advantage under these conditions.

Realizing all these possibilities, I felt that sufficient work had already been done in this country to justify a meeting of various interested workers devoted to discussion of past and future work. There is no need to enlarge on the great benefit accruing to medicine and public health from genetic studies. I might add that I consider it especially fitting that a conference on population genetics should be held in this country at this time. Population genetics is a discipline in whose name great outrages have been committed and possibly still can be committed. This is a field that has dangerous political implications, and this, I think, we population geneticists should realize.

To end, I would like to thank the Organizing Committee, Dr. Goldschmidt, Dr. Sheba, and Dr. Falk for the beautiful organization of the conference. I think I speak for all foreign participants when I say that we were enthusiastic about the welcome we have been getting and about the wonderful organization of all the little details that go into the conference.

SHEBA: Thank you very much, Dr. Motulsky. I would now like to call on Dr. Aharoni, who will present some data on our ancient history. You will agree that the population geneticist cannot afford to neglect historical facts.

Y. AHARONI

Recent Archeological Discoveries in the Judean Desert

It came as a surprise to me that I should be called upon to address an audience of geneticists on recent archeological finds. Naturally, I tried to understand what bearing my presentation could possibly have on the subject of this conference, which will deal with the diversification of the Jewish communities reassembling on this soil, from which they were scattered many generations ago.

I gather that human genetics as a discipline has a large stake in history. Insofar as it deals with short-range evolution in man, it attempts to trace the remote origins of modern human populations. The geneticist shares this interest in the past with the archeologist. In fact he regards archeology as the auxiliary science that may furnish him with important raw material for his reconstructions.

The geneticist who wishes to elucidate the ethnic affinities of the Jewish communities may be well advised to turn to archeology. Even a casual inspection of one of our great archeological sites, such as Hazor, Megiddo, or Beth Shaan, will convince him that this country has witnessed migrations, invasions, and retreats for many thousands of years. It was a transit station for caravans and for armies.

The outposts of each of the great civilizations of the Ancient World were stationed here during different periods. Wherever you search or dig in this country, you will find evidence that this was a meeting place of many cultures and you may infer that it must have been a melting pot of many ethnic groups.

I assume that such considerations may indeed have a bearing on your discussions regarding the origins of the Jewish tribes. A brief review of the discoveries at any of our archeological sites will give you some idea of the great complexity of historical events and population shifts in ancient Israel. It may prevent you from drawing rash conclusions by oversimplification of facts. A presentation of some recent discoveries in the Judean desert may be as good an introduction as any to the complexity of our ancient history.

The story started not really in Israel but in what is now Jordanian territory, at the northern end of the Dead Sea, with the discovery of the first of the famous Dead Sea Scrolls,[1] which are on display on the campus of the Hebrew University. When, later, we started a search for similar remarkable documents in our part of

1 Cross, F. M., Jr., *The Ancient Library of Qumran and Modern Biblical Studies*, 2d ed., Anchor Books, New York, 1961.

FIG. 1. The Bar Kokhba caves at Nahal Ze'elim. near Masada. Note the dark entrances into a series of caves on the face of the cliffs. (*Photograph by D. Harris*)

the Judean desert we felt by no means sure that further treasures would be in store for us.

Our finds were made on the western shore of the Dead Sea. The site lies on the coastal strip extending north of Massada, the fortress which was the last stronghold of Jewish resistance against the Romans at the time of the destruction of the Second Temple, toward En-gedi, the beautiful and fertile oasis in this dry desert region. The caves we searched are hidden high on the face of a cliff standing 500 to 600 meters above the level of the Dead Sea. (Fig. 1).

These cliffs and canyons above the Dead Sea are ideal hiding places and must have sheltered refugees and rebels from Judea throughout the ages. The moment you visit these caves you understand why David, fleeing before Saul, and others in earlier and later periods selected this area as a temporary abode. It was a potential base for raids into the heart of Judea, for a march of only a few hours led to the Hebron area, and Jerusalem was not much farther off.

If this truly remote corner of the country has recently become the center of attention of Israel's archeologists, the reason lies in the extreme dryness of the caves, which almost perfectly preserved organic materials from decay. These materials include garments and utensils made of leather and cloth and, most interesting of all, parchments and papyri. Some of the objects hidden in these caves, though two, three, and even four thousand years old, looked to the members of the expedition as though they had been abandoned only the day before, covered with the fine dust which adheres to any exposed surface in this area even after the first few hours.

To the Bedouin, who discovered almost all the caves on the northern shore of the Dead Sea, across the Jordanian border, this may be easy terrain. It was different for us without the advantage of local Bedouin guides. Figure 1 shows that the caves are on sheer cliffs, accessible only from above. It is only after climbing by narrow winding paths from the shore of the Dead Sea up to the first plateau of the Judean desert that one can descend the 50 or 100 meters to the mouths of the caves.

Starting in 1953, we had explored the area without any real assurance that the findings would warrant a large-scale effort.[2, 3] It was only on our fifth excursion, in January 1960, that we found the first written document (Fig. 2). It was a small fragment of phylacteries *(T'filin)* written in a perfect Hebrew script of the Bar Kokhba period (A.D. 135) and containing the first verses of Chapter 13 of the Book of Exodus. This find gave the impetus to two large-scale expeditions carried out in the spring seasons of 1960 and 1961.[4]

Each expedition consisted of four groups headed by three members of the Hebrew University staff, Profs. Yadin and Avigad and I and by Mr. Bar Adon of

2 Aharoni, Y., The caves of Nahal Hever, *Atiqot, J. Israel Dept. Antiquities, III,* 1961, 148-162.
3 Aharoni, Y., and Rothenberg, B., *In the Steps of Kings and Rebels,* Massada, Tel-Aviv, 1960.
4 Avigad, N., Aharoni, Y., Bar-Adon, P., Yadin, Y., Lifshitz, B., Rahmani, L. Y., Nathan, H., and Zaitschek, D. V., The expedition to the Judean Desert, *Israel Explor. J., 11,* 1960, 1-72.

the Department of Antiquities affiliated with the Israel Ministry of Education and Culture. We enjoyed the help of hundreds of volunteers and the full cooperation of the Army, which organized the four base camps.

The discoveries of these last expeditions belong mainly to two different eras. The earlier period is that which we call in Israeli archeology the Chalcolithic Age—the transition from the Stone Age to that of Copper and Bronze, at the end of the 4th millennium B.C. Radio-carbon datings for this early material point to about 3000 B.C. or perhaps a little earlier. One of the caves explored by Bar Adon yielded the outstanding Chalcolithic find of these expeditions. During the last days of that season, when the group had nearly despaired of success, a treasure-trove was found hidden beneath a slab of rock, containing more than 400 copper vessels as well as other objects. The objects were wrapped in a woven mat which clearly belongs to the Chalcolithic Age, and therefore the vessels, too, must be ascribed to this period—the dawn of civilization in the Middle East, the predynastic periods of Egypt and of Mesopotamia, the beginning of settlement and agriculture and of village and city life in this region. This treasure may well remain one of the most important discoveries dating back to this period.

Most of the 430-odd objects are made of copper, like the mace-heads, examples of which have been found on other Chalcolithic sites in this country, though never in such large numbers. Others are of hematite and ivory. Some of the vessels are of types completely unknown, either in this country or, as far as we can tell, in any other region in the Middle East. They will require much study and research before we shall be able to define them and understand their purpose.

The archeologist tends to interpret any object of unknown function as having served for ritual purposes. This may or may not be true of the rich carved ivories or the decorated bronze staffs reminiscent of royal or divine sceptres appearing in Egyptian paintings. Many of these objects are remarkably beautiful, displaying great mastery of technique and a peculiar grasp of animal anatomy (Fig. 3).

This treasure was hidden in a remote corner of the cave, perhaps by its owner, who could never return to retrieve it. We do not know, as yet, who these people were and where they came from, whether the objects were manufactured locally or brought to this country, probably from the north. There is no question that this treasure may teach us a great deal about the beginnings of civilization in Israel and the adjacent countries.

The period of Bar Kokhba, to which the remaining discoveries of this expedition belong, was almost 3000 years later. The site of these discoveries is Hever Canyon, on each side of which a Roman camp was found overlooking the entrances to the caves. Clearly these must have been the encampments for the siege of the rebels hiding in the caves below.

In order to reach one of these caves, you descend a small path, probably much as in ancient times, and climb down low "steps" till you are directly beneath the entrance; then you go up about 12 meters by rope ladders to the cave's mouth.

I am referring to the so-called "Cave of the Letters," where the fifteen famous letters of Bar Kokhba were found by Prof. Yadin's group. Opposite this cave, on the other wall of the canyon, is the "Cave of Horror," the excavation of which fell to my share during the last expedition. The name of this cave derives from the many skeletons discovered inside it. Upon entering, we came to a corridor, about 4 meters wide, 3 high, and some 65 meters long; we have managed to excavate most of it this last year. We found Chalcolithic material, but the Bar Kokhba

FIG. 2. Fragment of a phylactery from the Bar Kokhba period. (*Photograph by B. Rothenberg*)

remains are more interesting. Four coins, with the name "SHIME'ON" written in ancient Hebrew script on one side, and the inscription "YEAR TWO OF THE FREEDOM OF ISRAEL" or "JERUSALEM" on the other, confirm again that the Bar Kokhba movement had decided to start a new era in Jewish history.

We found about forty skeletons in the cave, not only of men but also of women and children. These remains are now being subjected to anthropological studies[5,6] by Dr. Nathan of the Anatomy Department, Hebrew University, and some of them are being studied for blood groups by Dr. Nelken. Their conclusions should be of particular interest to this audience.

Many interesting objects lay among these skeletons, such as arrowheads of iron

5 Nathan, H., The skeleton remains (the caves of Nahal Hever), *Atiqot, J. Israel Dept. Antiquities, III*, 1961, 165-175.

6 Nathan, H., The skeletons of the Nahal Mishmar Caves, *Israel Explor. J., 11*, 1961, 65-69.

complete with their shafts of wood and cane, and sandals, needles, and combs belonging to the women and children. Foodstuffs, such as dates, which are common in the Dead Sea area—at Jericho, En-gedi, and the southern end of the Dead

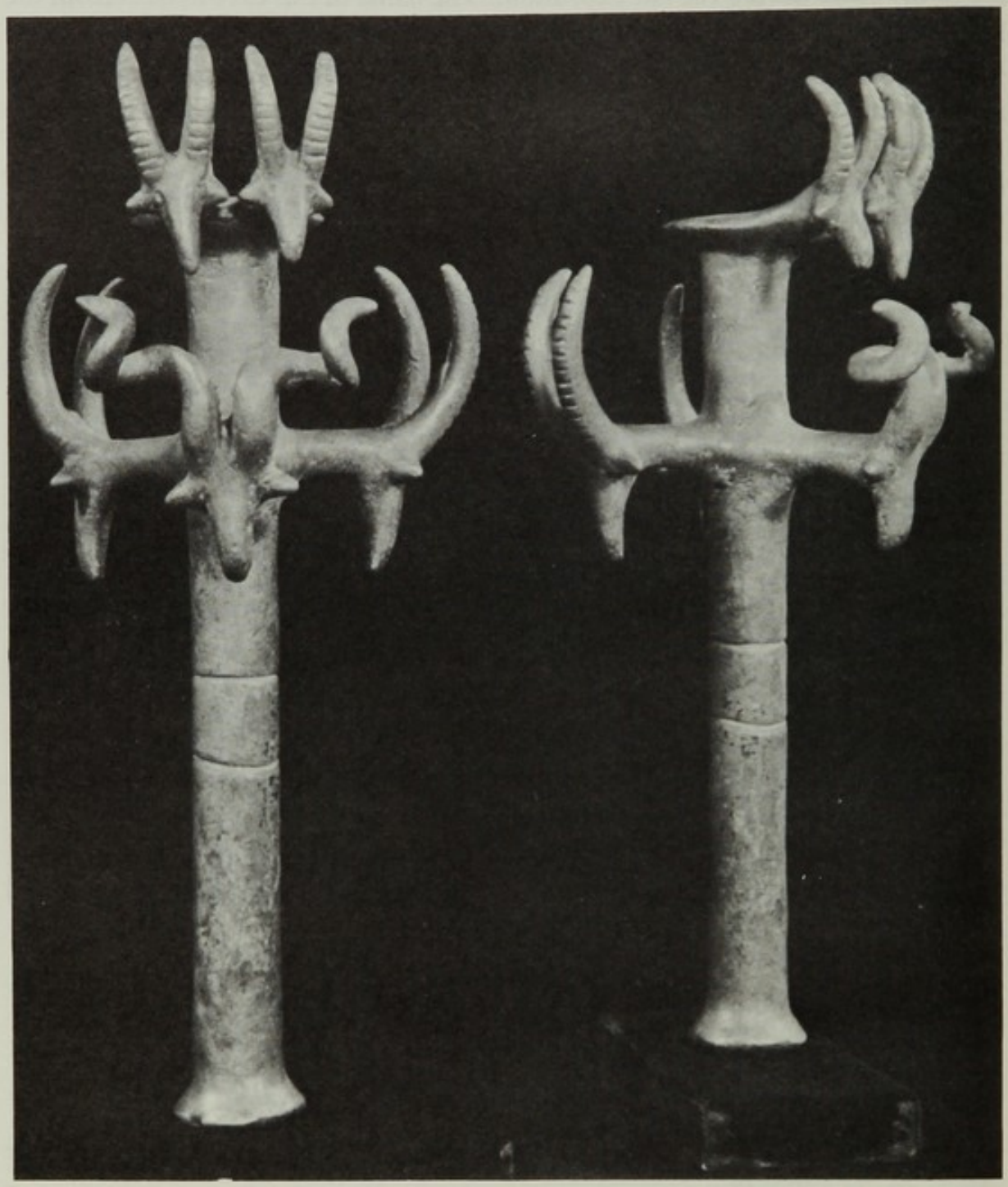


FIG. 3. One of the Chalcolithic copper objects from Nahal Mishmar, with its reflection (*right*) in a mirror. (*Photograph by J. Schweig*)

Sea—also came to light. Incidentally, the newer documents contain considerable material on the purchase and sale of date groves in this area.

The most interesting of the finds, however, were the many fragments of Hebrew and Greek papyri, recovered from beneath fallen rocks deep within the cave. One group includes fragments of the Twelve Minor Prophets, written on parchment, in Greek.

There are two interesting points to these last fragments. They belong undoubtedly to the same scroll as the fragments described in *Revue Biblique* in 1952,[7] and it is clear that one cave must have been visited some ten years ago. These small fragments also differ from the Greek translation as preserved in the Septuagint. For instance, the tetragrammaton is written in the ancient Hebrew-Phoenician script, unlike the Septuagint, which uses the Greek κυριος. Thus, we have here an early Jewish translation, unlike the accepted text of the Septuagint, which has been preserved by Christian scholars.

Some of the skeletons found in even the remotest corners of the cave were still wrapped in shrouds, and next to them lay shards inscribed with the names of the dead, such as "Shaul ben Shaul, Shalom"—Saul the son of Saul, Peace. All this indicates that there was enough time during the siege to bury at least some of the dead with due ceremonial.

One find, a small oil lamp, certainly did not belong to the Bar Kokhba period but dated from Byzantine times, some four or five hundred years later. Evidently neither we nor the Bedouins were the first to visit the caves after Bar Kokhba's rebels. From various sources we know that Byzantine monks were aware of ancient manuscripts hidden in the caves of the Judean Desert. One of them visiting our cave must have lost the lamp when it went out in the pitch black.

Of unusual interest were the many pieces of broken glass, from some of which two fine glass vessels could be restituted in the workshops in Jerusalem. The expert in charge of this work found himself unable to fit the fragments of one of these bowls into a perfect shape. We then recollected that these fragments had been picked up from a heap of ashes in the center of the cave, and we concluded that the vessel had obviously been deformed by the heat of fire. We thus obtained at least some hint concerning the last days of the besieged people in this cave.

It is quite certain that these caves could not be taken by military skill or force. However, as soon as their supplies were exhausted, the defenders were faced with the alternative of surrender or death from thirst and starvation. The intact state of the skeletons proves that these people had chosen the latter. On the last day, they probably built a fire in the middle of the cave and threw their more precious belongings into it.

The "Cave of the Letters" is situated on the opposite edge of the canyon. Professor Yadin found, in addition to twenty skeletons, a variety of utensils hidden away by the rebels in remote niches of the cave. Some of these objects were neatly packed in baskets, excellently preserved and revealing great craftsmanship. A basket weaver from Nazareth, where this type of basket is manufactured to this day, assured us that such high quality and perfect technique can no longer be found in the market.

We think that the bronze vessels packed in these baskets are Roman; the same styles may be seen in museums in Italy. Some of them are obviously meant for

7 Barthélemy, D., Rédécouverte d'un chainon manquant de l'Histoire de la Septante, *Revue Biblique*, 1953, 18-20.

ritual purposes. Many are decorated with human figures and faces. They may belong to the booty taken by the Jews from Roman legions during a more propitious phase of this desperate warfare.

The written documents constitute the most important of all the treasures found by Yadin in this cave. A bundle of fifteen papyri emerged in the first season, all from Bar Kokhba, some written in Hebrew, some in Aramaic, others in Greek, beginning mostly with the same salutation: "From Shime'on Bar Kosiba to the people of En-gedi . . . ."

During the past season, Yadin discovered another group of about forty papyri hidden in a basket in the same cave. All of them have been opened and their main contents revealed. The entire group belonged to a woman named Babta (a Hebrew-Aramaic name), who lived near the Dead Sea, sometimes at En-gedi, sometimes at Zoav, at the southern end of the Dead Sea. In Talmudic literature, Zoav is called the "city of palms," and, indeed, these documents mention that certain palm groves in this area belonged to Babta. Babta was quite a rich woman. She had much property, and she was involved in several lawsuits with various members of her family (she was married twice). These are, I believe, the first authentic Jewish legal documents discovered containing marriage and divorce contracts from the Mishnaic period—the time of Rabbi Akiva.

These documents prove clearly that the people who sought refuge in the caves were actually the main leaders of the community of En-gedi and the officials of Bar Kokhba in the area. This important oasis must have been a harbor and traffic center for connections of the Bar Kokhba rebels with Moab, Arabia, and Transjordanian Nabatea. In the final stages of the revolt, the inhabitants of En-gedi fled south to the remote caves in the cliffs. The Roman soldiers followed them into the desert, established their siege camps, and brought about the end as we discovered it 1800 years later.

Written fragments dating back to the period of the First Temple have been discovered in other caves of the Judean desert. They belong to the time of Jeremiah, about 600 to 700 B.C. We may therefore look to this desert to yield evidence on yet another period of military and cultural contacts established in the area.

I shall close this talk with a passage from Jeremiah: "Take these evidences [Hebrew "Sepharim"—written documents], this evidence of purchase . . . and put them in an earthen vessel, that they may continue many days. For thus saith the Lord of hosts, the God of Israel; Houses and fields and vineyards shall be possessed again in this land."

SHEBA: Dr. Aharoni has cast a spotlight on the link existing between population genetics and archeology. The history of the communities we are studying should be adequately known before inferences are drawn on selection or admixture. Keeping this lesson in mind throughout the five coming sessions of our conference, we shall feel induced to broaden the scope of our deliberations instead of confining ourselves to the facts that have already been confirmed in the test tube.

SESSION 1 A. E. MOURANT, *Chairman*

MIGRATION AND DRIFT IN POLYMORPHIC SYSTEMS

MOURANT: The general title of this morning's session is "Migration and Drift in Polymorphic Systems," to which I think I might add, in view of the title of Dr. Kalmus' paper, "natural selection."

Because of the opportunity offered by the unique genetic situation in Israel, considerable attention will be given to Israeli population genetics. The first paper this morning is by Dr. D. Nelken on "Blood Groups in Jewish Communities."

D. NELKEN

Blood Groups in Jewish Communities

The existing information on the blood groups of the various Jewish communities is due largely to the work of the late Prof. Gurevitch and his collaborators.[1-7] He felt that the gathering of exiles from all over the world offered a unique opportunity for anthropological studies—an opportunity which had to be seized before the communities merged. Blood-group data on 3500 individuals from ten communities were collected by the team in Jerusalem. Table I (see also p. 256) shows the main results concerning the ABO, MN, and Rhesus systems.

The visitor to Israel is usually struck by the marked differences in the external appearances of the various Jewish groups. It is difficult to decide how many of these seemingly distinctive features may be ascribed to apparel and hairdress, to nutrition or sun exposure, and to traditional demeanor, which shapes figures as well as faces. However, the blood-group studies have revealed certain striking differences among the Jewish communities. These are undoubtedly genetic, but this audience need not be reminded that they may, nevertheless, reflect selective influences of environmental agents which have been at work for many generations.

Considering first the ABO system, we find a high frequency of O in the Jews from Yemen and Cochin. There is less variation among the other communities. The Jews from North Africa (Morocco, Tunisia, and Tripolitania) resemble the

1 Gurevitch, J., Hasson, E., and Margolis, E., Blood groups in Persian Jews, *Ann. Eug., 21,* 1956, 135-138.

2 Gurevitch, J., Hasson, E., Margolis, E., and Poliakoff, C., Blood groups in Jews from Tripolitania, *Ann. Eug., 19,* 1955, 260-261.

3 Gurevitch, J., Hasson, E., Margolis, E., and Polishuk, Z., Blood groups in Jews from Cochin, India, *Ann. Human Gen., 19,* 1955, 254-256.

4 Gurevitch, J., Hermoni, E., and Margolis, E., Blood groups in Kurdistani Jews, *Ann. Eug., 18,* 1953, 94-95.

5 Gurevitch, J., Hermoni, E., and Polishuk, Z., Rh Blood types in Jerusalem Jews, *Ann. Eug., 16,* 1951, 129-130.

6 Gurevitch, J., and Margolis, E., Blood groups in Jews from Iraq, *Ann. Human Gen., 19,* 1955, 257-259.

7 Margolis, E., Gurevitch, J., and Hasson, E., Blood groups in Jews from Morocco and Tunisia, *Ann. Human Gen., 22,* 1957, 65-68.

Sephardim in their ABO concentrations but appear to possess slightly higher frequencies of both O and B. The ABO frequencies of Sephardim and Ashkenazim are quite similar to those of certain European populations.

The Rhesus system varies strikingly among the various Jewish tribes. The frequency of Rh negative individuals ranges from 4 to 17 percent, and this has a bearing on Rh incompatibility, which is very rare in many of the Oriental communities. It is interesting to note that the Rhesus system indicates marked differences between the Jews from Yemen and those from Cochin, who appeared to resemble each other in their ABO frequencies. In most of the communities, the CDe chromosome, sometimes called the Mediterranean chromosome, is represented in rather high concentrations.

TABLE I

THE COMMON BLOOD-GROUP SYSTEMS IN TEN JEWISH COMMUNITIES

Community	O	A	B	M	N	CDe	cDE	cDe	cde	*Rare chromosomes*
Yemen	72.4	18.5	9.1	75.6	24.4	56.1	7.9	6.4	28.2	1.4
Cochin	73.1	10.1	16.8	60.6	40.0	41.5	5.0	6.2	44.4	2.9
Baghdad	49.3	30.1	20.6	60.5	39.5	53.5	15.8	4.1	19.8	6.8
Kurdistan	51.2	32.0	16.8	52.9	47.1	53.0	17.9	5.2	15.0	8.9
Persia	55.0	26.5	18.5	59.2	40.8	60.5	10.9	6.0	22.7	0.0
Morocco	62.2	23.1	14.7	55.9	44.1	53.4	6.3	9.4	30.8	0.1
Tunisia	62.9	21.2	15.9	55.5	44.5	56.1	6.6	8.5	28.4	0.4
Tripolitania	62.4	21.2	16.4	50.5	49.5	43.0	7.8	9.5	36.4	3.3
Sephardim	54.4	32.1	13.5	50.0	50.0	46.8	8.6	11.0	26.4	7.2
Ashkenazim	61.6	26.2	12.2	63.5	46.5	51.5	12.1	5.2	30.4	0.8

The frequency of the cDe chromosome, also called the African chromosome, does not rise above 11 percent in any of the communities and is much rarer in some of these groups. Nevertheless, it has been pointed out that in the frequency of this chromosome the Jewish communities resemble Near East populations and differ from most European populations.

It is well known that Prof. Gurevitch and his collaborators presented their data without offering any interpretations. Dr. Mourant has utilized these data in his comprehensive comparisons,[8,9] and is responsible for several suggestions concerning the affinities among the various Jewish tribes. In many cases he was able to show that the similarities between the Jews and their non-Jewish neighbors were not as complete as they seemed at first. At the same time, he refrained from final conclusions until they could be based on a larger number of polymorphic systems.

8 Mourant, A. E., *The Distribution of the Human Blood Groups*, Blackwell Scientific Publications, Oxford, 1954.

9 Mourant, A. E., The blood groups of the Jews, *Jewish J. Sociol., I*, 155-176.

SINGER: Dr. Nelken indicated that it was possible to differentiate individuals of various Jewish communities on the street, and he also hinted that the ABO differences reflected the physical differences of the Jewish communities. Could you please tell me, Dr. Nelken, whether the physical differences you observed were based on medical or nonmedical data or both or merely on subjective observations?

NELKEN: I did not mean to imply that there is a straight relationship between physical appearance and blood-group frequencies. But many feel that there must be a physical-anthropological basis to the "types" that seem to them representative of the various Jewish communities. Lacking extensive studies on the physical anthropology of the communities, these opinions remain subjective. We are certainly not in a position to correlate the data of physical and biochemical anthropology; the latter are far from complete and the former are exceedingly scanty.

MOURANT: Thank you, Dr. Nelken, for your most interesting paper and for your kind remarks about me. If he will allow me to say so, Dr. Nelken has, perhaps, telescoped my attempts at interpretation, and I do not think I would express them exactly as he has.

The next paper, by Dr. B. S. Blumberg, is "Polymorphisms of the Human Serum Proteins and other Biological Systems."

BARUCH S. BLUMBERG

Polymorphisms of the Human Serum Proteins and other Biological Systems

The purpose of this paper is to present data on polymorphic systems other than the blood groups which can be used for the genetic description of populations. Populations may be described by their gene pools—that is, the total number of alleles distributed among the members of an interbreeding group—and by the interaction of the genes and their products with one another and with the environment. There are several gene loci at which variation occurs in many populations. These may be helpful in anthropological studies if the frequencies of the alleles vary among populations. There are other gene loci at which the variation seems to occur in only one or a few populations, and traits of this kind are particularly useful. Examples of these are the Diego, Hunter, Henshaw, and Vel blood groups, and some of the Gm serum gamma globulin groups.

Ideally, the frequency of the alternate alleles at each variable locus could be determined, and the resultant figures would provide a type of statistical description of the population. Mutual interaction of the genes with one another and with the

environment must also be considered in the biological description of the group. With this concept, the often debated question of how many human races exist is reduced to the level of a statistical decision as to how much variation at how many gene loci is required for establishing an acceptable distinction.

Genes that conform to the definition of polymorphism are suitable for the gene-tally methods. According to Ford,[1] polymorphism is the occurrence in the same habitat of two or more discontinuous forms of a species in such numbers that the rarest form cannot be maintained by recurrent mutation alone. In polymorphic systems which fit this definition, the phenotypes are common in the population. It is usually not necessary to study enormous samples to arrive at good approximations of gene frequencies. The phenotypes are discrete, and classification is apparent. In many cases, the genotype may be inferred directly from the phenotype and heterozygotes may be determined. Some quantitative traits whose phenotypes are not completely discrete may be used if a diphasic or multiphasic distribution is obtained in a population survey. Examples of these are the urinary excretion of BAIB, the taste of phenylthiocarbamide, and the isoniazid inactivation trait.

Selection is a powerful agent in the maintenance of polymorphisms, and the nature of this force, as well as mutation, genetic drift, and other factors, will undoubtedly be discussed during this and other sessions. Selection pressures can vary enormously in different environmental conditions, at different times, and in populations with different gene pools. At one extreme there may be genetic systems which are selectively neutral; these would constitute the "nonadaptive" traits favored by anthropologists. Some authorities deny the existence of such traits. At the other extreme, selection may be intense, with marked changes over the course of only a few generations. The traits for which selection is least intense would seem to be the most satisfactory for the comparison of populations. But even those traits that are subject to selection indicate the peculiar environmental experiences of a population and are therefore characteristic of the group. The comparison of many polymorphic traits is probably the best method currently available for the adequate distinction of populations. I shall discuss some of the polymorphisms that have been found useful in this work.

The haptoglobins are a family of serum proteins which bind hemoglobin, and several distinct types can be distinguished by starch gel electrophoresis. The three common types are 1-1, 2-1, and 2-2. They are shown in strips *a*, *b*, and *c* of Figure 4. Several rare variants are also known (strips *d*, *e*, *f*, *g*), including one in which no haptoglobin is seen (ahaptoglobinemia, strip *d*). The common haptoglobin phenotypes are determined by two allelic genes, Hp^1 and Hp^2. Another gene, Hp^{2M}, has also been described, and studies on the genetics of this trait have been published.[2]

Figure 5 shows the distribution of both the Hp^1 gene and the ahaptoglobinemia

1 Ford, E. B., *Genetics for Medical Students*, Methuen, London, 1956.

2 Giblett, E., and Steinberg, A. G., The inheritance of serum haptoglobin types in American Negroes: evidence for a third allele, Hp^{2M}, *Am. J. Human Gen.*, *12*, 1960, 160-169.

phenotype. The data were collected from several sources, including a recent compilation,[3] and some general inferences can be made from them. There is a striking uniformity in the distribution ot the phenotypes in most European populations. There is a very high frequency of Hp^1 in most African populations, particularly in West Africa, and a low frequency in Asian populations. There appears to be a north-south gradient of increasing Hp^1 frequency in Europe-Africa and the Americas but, so far as can be seen, not in Asia.

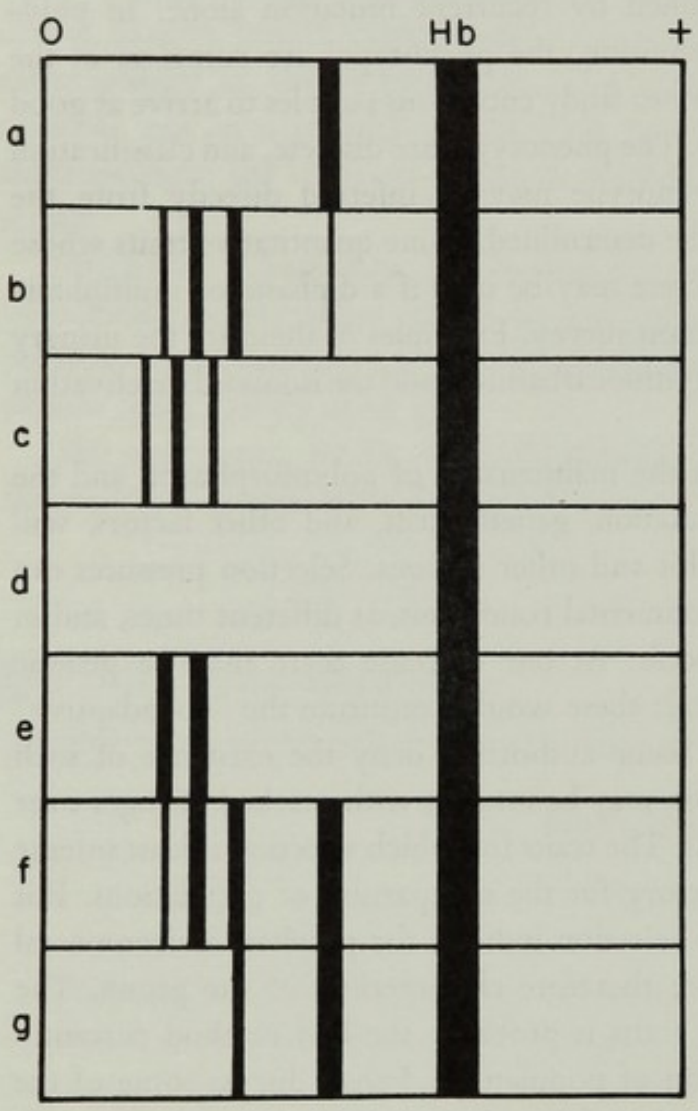


FIG. 4. Diagram of the electrophoretic mobility of the haptoglobin bands in starch gel. Types 1-1, 2-1, and 2-2 are shown in strips *a*, *b*, and *c*, respectively. Strip *d* shows the type 0 phenotype; the remaining strips are rare phenotypes. 0: origin, Hb: excess hemoglobin band, +: positive pole.

I would like to consider the haptoglobin O phenotype—the hypohaptoglobin or ahaptoglobin type. Dr. Allison, Mrs. apRees, and I first described ahaptoglobinemia in apparently normal individuals (not newborns) in a Nigerian population.[4] Approximately 30 percent of the 99 individuals studied were of this phenotype; subsequent quantitative studies have indicated somewhat lower frequencies. It is now known that some cases of ahaptoglobinemia may be inherited, and Dr. Steinberg has studied this problem. Some cases may be due to diseases in

3 Sutton, H. E., Matson, G. A., Robinson, A. R., and Koucky, R. W., Distribution of haptoglobin, transferrin, and hemoglobin types among Indians of Southern Mexico and Guatemala, *Am. J. Human Gen.*, *12*, 1960, 338-347.

4 Allison, A. C., Blumberg, B. S., and apRees, W., Haptoglobin types in British, Spanish Basque and Nigerian African populations, *Nature*, *181*, 1958, 824-825.

which there is a breakdown of red blood cells, as in the hemolytic anemias, with consequent temporary exhaustion of the serum haptoglobin levels due to formation of haptoglobin-hemoglobin complexes.[5,6] Some cases may occur spontaneously with no apparent cause. We studied three Micronesians who at one time were of haptoglobin type 2-2, but, when examined two years later, were not typable. Complete medical and hematological examinations were performed at both times, and there was no apparent illness.[7]

FIG. 5. The prevalence, in percent, of the *Hp*1 gene. The percent of ahaptoglobinemics is shown in parentheses.

In Africa, the area of high frequency of the ahaptoglobinemia phenotype corresponds to the belt of distribution of *falciparum* malaria. This suggests that low haptoglobin levels may be associated with the hemoglobinemia that occurs with malaria. In collaboration with Dr. Kuvin, Dr. Beye, Dr. Robinson, and Mr. Teitelbaum, we studied the serum haptoglobin levels in patients with several forms of experimental malaria. During the acute attack there was a marked decrease in serum haptoglobin. The haptoglobin levels returned to normal in the convalescent period. It is not yet known whether this could explain the low haptoglobin levels found in areas where chronic malarial infection is common.

The transferrins (serum iron-binding proteins) constitute another polymorphism useful in describing populations.[8] Europeans are nearly always of the C phenotype. The slower migrating D phenotype and the heterozygous CD phenotype

5 Allison, A. C., and apRees, W., The binding of haemoglobin by plasma proteins (haptoglobins), *Brit. Med. J., ii,* 1957, 1137-1143.

6 Alurell, C. B., and Nyman, M., Studies on the serum haptoglobin level in hemoglobinemia and its influence on renal excretion of hemoglobin, *Blood, 12,* 1957, 493-506.

7 Blumberg, B. S., and Gentile, Z., Haptoglobins and Transferrins of two tropical populations, *Nature, 189,* 1961, 897-899.

8 Giblett, E., and Blumberg, B. S. (ed.), *Proceedings of the Conference on Genetic Polymorphisms and Geographic Variations in Disease,* Grune & Stratton, New York, 1962.

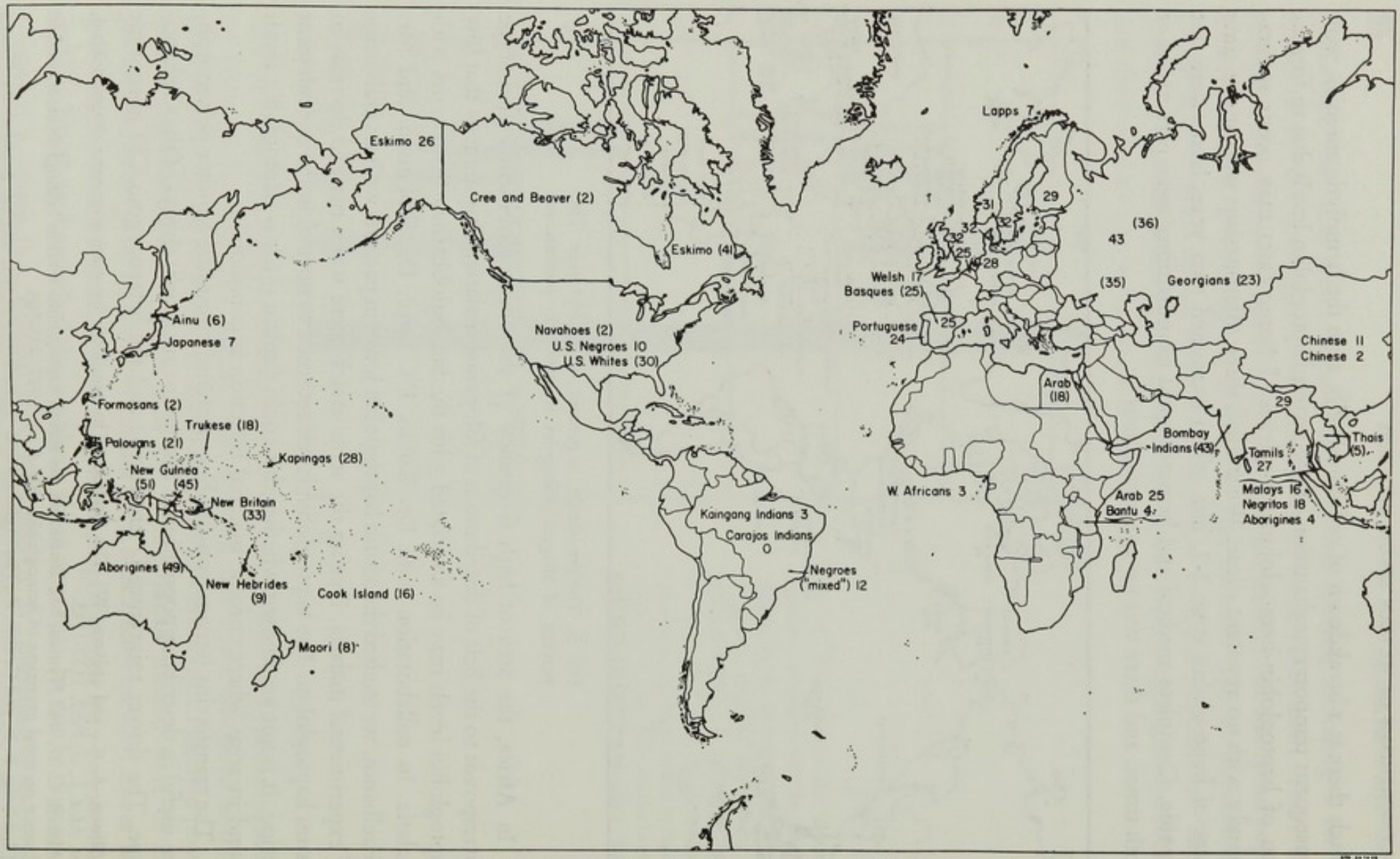


FIG. 6. The prevalence, in percent, of the phenylthiocarbamide (PTC) nontaster phenotype.

are found in Africans, Australian aborigines, and other populations. The fast-moving B and heterozygous BC phenotypes are rare in most populations but are found in a few Europeans and Orientals. In addition to these major transferrins, there are bands of different mobilities whose distribution and genetics are still being studied.

The taste polymorphism has been known since 1931. Some people can taste phenylthiocarbamide (PTC) and others cannot. Individuals who are homozygous for a recessive gene *t* are nontasters; those who are homozygous for its dominant allele *T* or who are heterozygous are tasters. PTC tasting is a threshold phenomenon—most "nontasters" can taste it if they are given enough of the substance. A wide variety of compounds related to PTC can also be used to exhibit the taste dimorphism. These are characterized by the NCS chemical linkage, and many of these compounds are goitrogenic. Several studies have shown an association between this polymorphism and some forms of thyroid disease.

Figure 6 shows the distribution of nontasters in the world's populations. Several general observations may be made. There is a low frequency of nontasters in American Indians and in Asian populations. Eskimos, however, have frequencies strikingly different from those found in American Indians. There is a high frequency of nontasters in India. The low frequency in Africa south of the Sahara is reflected in the low frequency among U.S. Negroes. Lapps have a low frequency compared to other Scandinavian populations. And the Welsh, who may be an example of what Dr. Boyd refers to as Old European, have a lower frequency than the other European populations tested. Most Jewish populations have a low frequency, but it is higher in Cochin Jews and Jews from the island of Gerba (see p. 281).

Another nonserological polymorphism is the urinary excretion of beta-amino-isobutyric acid (BAIB). This is probably a polygenic trait with most of the variation controlled by a single gene. Individuals who are homozygous for a recessive gene are high excretors; homozygotes for the alternate allele and heterozygotes are low excretors. The frequency of high excretors is low in Europeans and high in many nonwhite populations, including the American Indians, Africans, and the two small samples of Japanese and Chinese studied thus far. A rather striking finding was the high frequency in Marshall Islanders, a frequency not reflected in other Oceanic peoples, such as the Tahitians, New Guineans, Javanese, and Vietnamese.[9] Several factors known to elevate BAIB excretion in humans are X radiation, leukemia, cancer, and various kinds of antileukemia therapy. Some of the inhabitants of Rongelap had been subjected to considerable fallout five years before the collection of the specimens, but there was no indication that this was the cause of the high BAIB excretion. Random drift may have operated to produce the high BAIB frequencies in this island population.

[9] Blumberg, B. S., and Gartler, S. M., Urinary excretion of beta-amino-isobutyric acid in Pacific populations, *Human Biol.*, 1962. In press.

To conclude, I should like to discuss a polymorphism discovered in our laboratory.[10] A patient who had received approximately fifty transfusions for a refractory anemia developed an antibody which, in an Ouchterlony gel diffusion system, reacted to form a precipitin with the serum of some individuals. Individuals with gene Ag^A in single or double dose were reactors; those who were homozygous for its alternate allele Ag were not. It was subsequently found that the protein which reacted with the antibody in the patient's serum was a low-density (beta) lipoprotein.[11] The distribution of the trait in several populations has been determined (Table I). The frequency varies widely. All of 99 Polynesians

TABLE I

DISTRIBUTION OF Ag^A PHENOTYPES IN VARIOUS POPULATIONS

Population	*Total no.*	*Positive*		*Negative*		*Frequency of Ag^A gene*
		No.	*%*	*No.*	*%*	
Polynesians, Bora Bora	96	96	100	—	—	1.00
Micronesians, Rongelap Atoll	101	95	95	6	5	.78
Eskimos, North Alaska	97	79	81	18	19	.56
Vietnamese	99	70	71	29	29	.45
Athabascan Indians, Alaska	102	69	68	33	32	.43
U.S. Negroes	167	92	55	75	45	.33
U.S. Whites	188	103	54	85	46	.32
Arabs, Israel*	39	28	71.8	11	28.2	.47
Kurdish Jews*	17	12	70.6	5	29.4	.46
Persian Jews*	37	26	70.3	11	29.7	.46

* Preliminary results.

from Bora Bora were reactors, whereas approximately 50 percent of U.S. individuals reacted. There were intermediate frequencies in other populations. With the help of Dr. Sheba and Dr. Ramot we studied the frequency of reactors among Israelis (asterisks in Table I). There appeared to be no difference in the reactor frequencies of the three groups studied.

MOURANT: Thank you, Dr. Blumberg. Dr. Blumberg will take the Chair while I present my paper.

BLUMBERG: The next speaker will be Dr. Mourant, who will discuss "Blood Groups in Southwest Asia."

10 Allison, A. C., and Blumberg, B. S., An isoprecipitin reaction distinguishing human serum protein types, *Lancet, i,* 1961, 634-637.

11 Blumberg, B. S., Dray, S., and Robinson, J. C., Antigen polymorphism of a low density β-lipoprotein. Allotypy in human serum, 1962. In preparation.

A. E. MOURANT

Blood Groups in Southwest Asia*

Fairly comprehensive data are available on blood-group frequencies in some, though by no means all, of the countries surrounding the Mediterranean Sea. Data for India are also quite extensive, though far from adequate in relation to the anthropological complexity of its populations. It is clear, however, that, despite considerable differences in some respects, there are certain important similarities between the blood-group frequencies found in Mediterranean countries and those of the settled (as distinct from the tribal) populations of India. For the intervening region of southwest Asia, however, data are most inadequate, and therefore we do not know how fully the features in which Mediterranean and Indian populations resemble one another are maintained or how and where the differences that separate the populations of the two regions arise.

Southwest Asia and the adjacent region of northeast Africa form an area which witnessed the origins of civilization. In early times (and to some extent since) it undoubtedly witnessed most of the great population movements between the continents. An understanding of these movements is vital to the explanation of the present population distributions in Asia, Africa, and Europe.

The high mountain ranges which characterize the region restrict human communications and population movements. The greatest barrier, however, is the almost impassable Great Salt Desert of central Iran. Partly because of such geographical barriers, the populations of the region are divided into many ethnic groups.

Politically the region is divided into several independent states. In some cases, members of a single group are found in several states. Many physical-anthropological studies of these groups have already been done. Because of the ethnic complexity of the region—much of it certainly reflected in physical racial characteristics—it is likely that the ultimate blood-group maps will be highly complex. On the other hand, it may be that similarities in blood-group frequencies will reveal important physical relationships among ethnic groups (or, in some cases,

* The facts summarized in this paper are drawn from a very large number of original papers, many of which are not now easily accessible. The data contained in the earlier papers have been tabulated for the most part in two books: Mourant, A. E., *The Distribution of the Human Blood Groups,* Blackwell Scientific Publications, Oxford, 1954, 438 pp., and, Mourant, A. E., Kopeć, A. C., and Domaniewska-Sobczak, K., *The ABO Blood Groups: Comprehensive Tables and Maps of World Distribution,* Blackwell Scientific Publications, Oxford, 1958, 276 pp. These books also provide full bibliographic references. Papers will therefore be listed in the footnotes of this contribution only if they contain data that are not tabulated in these books or if it is necessary to make specific reference to them. For bibliography on blood groups of Jews see pages 18 and 19.

will confirm such relationships already suspected on anthropometric or other grounds).

We already have considerable information on blood-group distribution in southwest Asia, but certain parts of the region have hardly been investigated, and for other parts our information is seriously incomplete. The purpose of this paper is to summarize the existing information, to show its relation to the information on blood-group distribution in some adjacent regions (as well as to our even more scanty information on some other parts of Asia), and, finally, to show what I think are the most profitable directions for future investigation.

One aspect of the anthropology of the region which interests us particularly relates to the fact that it saw the rise of the Jewish people and that until recently it contained many dispersed Jewish communities. I have already pointed out the importance of knowing the blood-group distribution in the region as an aid to the interpretation of the extensive data now becoming available in Israel on the blood groups of various Oriental Jewish communities[1] (see also pp. 256-263).

The ABO Blood Groups

Only the ABO blood groups have been studied sufficiently to enable us to see an over-all distribution pattern in southwest Asia. It is well known, however, that, in European areas and elsewhere where Rh and MNS distributions as well as ABO have been studied, the ABO system shows the most marked fluctuations. It is therefore not surprising to find a wide range of ABO frequencies in southwest Asia.

In Turkey[2] we find very high frequencies of group A—more than 30 percent throughout most of the country. This value is exceeded over only a relatively small part of Europe. The Turkish-speaking peoples farther east have frequencies of A which are relatively high but not so high as in Anatolia. The Armenians, however, wherever they are now found, show very high A frequencies, exceeding on the whole those of the Turks. The frequency of B among Turks is distinctly low compared with values in most of Asia, most Turkish populations tested having between 10 and 15 percent of B genes.

As we go south from Turkey, the frequency of A falls steadily until we reach Arabia, with mostly less than 15 percent of A genes. B, on the other hand, first rises as we go south to Syria and Lebanon,[3] then falls steadily, reaching very low values in southern Arabia. Indeed, the low A and very low B frequencies found in the Arabs of Nejd, Hadramaut, and Yemen are not unlike those of the more extreme northwest Europeans, such as the Scots and the Irish, and of the Berbers of Morocco.

Farther east the same zones continue, on the whole, to be recognizable, but the

1 Mourant, A. E., The blood groups of the Jews, *Jewish J. Sociol., 1*, 1959, 153-175.
2 Aksoy, M., Ikin, E. W., Mourant, A. E., and Lehmann, H., Blood groups, haemoglobins, and thalassaemia in Turks in Southern Turkey and Eti-Turks, *Brit. Med. J., 2*, 1958, 737-739.
3 Nassif, R. E., The incidence of blood groups in Lebanon, *Lebanese Med. J.*, 1953, 346-349.

Turkish-speaking peoples and the other peoples of the southern part of the Soviet Union do not show quite as high A frequencies as do the Turks of Anatolia and the Armenians. There is, moreover, a steady increase in B frequencies, culminating in the very high levels found in the northern part of the Indian region.

The MNS System

The frequency of the M gene is high, mostly well above 60 percent, in nearly every Indian population tested, whereas it is below 60 percent and mostly below 55 percent in the Mediterranean area, apart from Sardinia. Insofar as the scanty data available allow us to judge, there appears to be a sudden rise from low, typically European and Mediterranean M frequencies in Turkey[4] (both in Turks and in Eti-Turks) and Lebanon[5] and in the Armenians, to much higher values in Syria, Arabia, Iraq, and Iran.[6] Egyptians show low, typically Mediterranean frequencies, but higher values occur in Sudan, Ethiopia, and Somalia, where they appear on the map as an extension, unique in Africa, of the high M area of Asia.

Even less is known of the distribution of the associated S and s genes in southeast Asia. Throughout Europe, and also in India, S is linked with M rather than N, and high M frequencies tend to be associated with high S frequencies. This applies to the Yemenite Arabs but not to the Zabidi Arabs. No other data on S frequencies in non-Jewish peoples are available for the area under examination. High S frequencies extend into Africa among the Ethiopians, and to a lesser degree in the Kikuyu and Iraqw[7] of Kenya, and in the Northern Sudanese.

The MNSs pattern shown by these relatively few data is most suggestive, and further data, when they become available, are likely to be of great anthropological interest.

The Rh Groups

Because of the clinical importance of the Rh groups, rather more is known about their distribution in the region than about the MNSs groups, but much of the information refers solely to the simple distinction between positives and negatives. Unlike the ABO and MNS groups, the Rh groups show only small frequency differences between the Mediterranean area and India, though there is a tendency for frequencies of the cde gene complex and of Rh negatives to be lower, and of CDe and Rh positives to be higher, in India than in the Mediterranean area.

In the intervening region of southwest Asia there is a general conformity of Rh frequencies to the common Mediterranean-Indian type of distribution, but the variations revealed by existing data do not show any well-defined pattern. Their

4 Aksoy, M., *et al.*, *op. cit.*
5 Nassif, R. E., *op. cit.*
6 Boué, A., and Boué, J., Étude sur la répartition des groupes sanguins en Iran, ii, *Ann. Inst. Pasteur, 91,* 1956, 898-911.
7 Allison, A. C., Ikin, E. W., and Mourant, A. E., Further observations on blood groups in East African tribes, *J. Roy. Anthrop. Inst., 84,* 1954, 158-162.

interpretation is, moreover, complicated by the known presence of considerable frequencies of the gene complex cD^{u}e in the eastern Mediterranean region. It is now realized that unless the conditions of testing and the specificity of the reagents used are very carefully controlled, there may be confusion either between d and D^u or between D^u and D, or perhaps both.

It is clear, however, that the lowest frequencies of Rh negatives are not confined to areas on the borders of India. Some of the lowest frequencies reported are from Lebanon and southern Arabia, and almost the lowest of all those recorded are for Cypriots,[8] both the Greek-speaking and the Turkish-speaking communities having much lower frequencies than the peoples of either Greece or Turkey.[9, 10]

Despite the variety of populations living in Iran, with markedly different ABO frequencies, there is relatively little variation among the many sets of Rh frequencies determined by Boué and Boué.[11] The frequency of Rh negatives tends to be low—lower on the whole than in northern India, except in the Kurds, and in the Turkish-speakers of Akinlou, Hamadan province. It is low in the other Turkish-speaking communities, though, as mentioned, relatively high in Turkey itself.[12-14]

Other Blood-group Systems

Very little indeed is known of the distribution of the blood groups of systems other than ABO, MNSs, and Rh. For the Lutheran (Lu^a) gene, Turks and Eti-Turks[15] have frequencies near those found in western Europe. The gene is absent from all populations tested in the Indian region except the Veddahs[16] of Ceylon. The frequencies of the Kell (K) gene in Turks is low in comparison with Europe, and in Eti-Turks lower still. Both frequencies fall within the wide range reported for the Indian region, but the gene appears to be absent from Mongoloid peoples.

The frequency of the Duffy (Fy^a) gene is remarkably uniform throughout Europe (apart from the Lapps), gene frequencies ranging from 36.7 to 45.1 percent and mostly lying between 40 and 43 percent. Most figures reported for India are over 70 percent and those for eastern Asia higher still. The Turks and Eti-Turks have frequencies near the upper limit of the European range, whereas the Moslems of Teheran, Iran,[17] have 58 percent of Fy^a genes, a figure about midway between those for Europe and those for India.

8 Haddad, F. S., Blood groups in Cyprus and the Near East, *Brit. Med. J., ii,* 1958, 1415.
9 Mizan, N., 5272 Vak'ada kan gruplari ve Rh factörü, *Micobiol. Dergisi, 12,* 1959, 1-2, 9-10.
10 Sevgen, B., and Mizan, N., Türkiyede kan gruplari ve Rh factörü, *Tip Fakültese Mecmuasi'nin, Istanbul, 23*:3,1960, 560-563 (English summary).
11 *Loc. cit.*
12 Aksoy, M., *et al., op. cit.*
13 Mizan, N., *op. cit.*
14 Sevgen, B., and Mizan, N., *op. cit.*
15 Aksoy, M., *et al., op. cit.*
16 Wickremasinghe, R. L., Ikin, E. W., Mourant, A. E., and Lehmann, H., The blood groups and haemoglobins of the Veddahs of Ceylon, *J. Roy. Anthrop. Inst.,* 1962. In press.
17 Boué, A., and Boué, J., *op. cit.*

There appear to be no data available on the frequencies in southwest Asia of the P, Lewis, Kidd, or Diego blood groups, or of the ABH secretor phenomenon. It is most important that the limits of the range of the Di^a gene should be ascertained, especially as it has now been found in the Baltis[18] in the northwestern part of the Indian region.

Other Genetic Systems

Although we know a great deal about the distribution of the hemoglobinopathies in the Mediterranean area and in India, we know relatively little about these in southwest Asia. There are, however, important published data on Turkey, Iran, and southern Arabia, and we may hope that further data on Arabia and Iraq will be published shortly. For the recently discovered polymorphic serum factors, such as the haptoglobins, transferrins, and Gm groups, there appears to be no information. For Glucose-6-Phosphate-Dehydrogenase deficiency, so relatively common in Oriental and Sephardic Jews, the only non-Jewish data known to me come from Iran.

Blood Groups in Jews

Recently I attempted to collect and summarize all available data on Jewish blood groups.[1] Unfortunately, there are few new data[19-22] to be added to those which I collected. In discussing blood-group frequencies among Oriental Jews, some of which lie outside the ranges known either for other peoples of southwest Asia or for other Jews, I pointed out the need for further data on the autochthonous peoples of the region we are now discussing, including the southern parts of Soviet Asia, before we could ascertain the physical contribution made by these to the Jewish populations that live or formerly lived in the region. From some of the countries concerned we may hope to have new relevant data shortly, but for others the collection of evidence appears likely to be a very slow process.

It is most important that we should have new data on most of the blood-group systems and on other genetic factors from southwest Asia. This would not only help in the general interpretation of the anthropology and the population genetics of the region itself but would throw light on a much wider area. It would also expedite the interpretation of the findings being made on the Jews from these

18 Clegg, E. J., Ikin, E. W., and Mourant, A. E., The blood groups of the Baltis, *Vox Sanguinis, 6,* 1961, 604-614.

19 Gurevitch, J., Hasson, E., Margolis, E., and Poliakoff, C., Blood groups in Jews from Tripolitania and Cochin, India, Fifth International Congress on Blood Transfusions, Paris, 1954, 250-253.

20 Margolis, E., Gurevitch, J., and Hermoni, D., Blood groups in Sephardic Jews, *Am. J. Phys. Anthrop., 18,* 1960, 197-199.

21 Margolis, E., Gurevitch, J., and Hermoni, D., Blood groups in Ashkenazi Jews, *Am. J. Phys. Anthrop., 18,* 1960, 201-203.

22 Silberstein, and Goldstein, H., Blood groups in women of various oriental Jewish communities, *Harefuah, 54,* 1958, 295-296 (Hebrew with English and French summaries).

areas. For instance, the Kurdistan Jews have a very high B frequency, which appears to be higher than that found in the Kurds themselves, and it may be that if fuller studies were done in Kurdistan and the surrounding area, we should have an explanation of this. I offer this as a minor example of the many sorts of problems that crop up.

In the last few days I have been very much struck by the possibilities of studying the minorities in Israel itself. I had not realized that there were so many and so anthropologically interesting minorities here, and I am quite sure that the blood-group geneticists in Israel, as well as other human geneticists, are fully aware of the importance of studying these.

I wonder to what extent there are any really old Jewish populations in this country who might conceivably be genetically representative of the original Jews of the Diaspora. I throw out this suggestion in complete ignorance. Something has been said about groups of Jews who, at any rate, have lived here for many hundreds of years, and I wonder if there is any likelihood that these might be in any way representative of the original Jewish population.

Another point I should like to stress is the importance of the continuing genetic study of the Jewish communities now settled here, which I know is very much in the minds of all of the people of Israel here today. It seems to me that, in spite of the intermarriage that is taking place—and perhaps even these intermarriages might themselves be a particular subject for study—there is here a unique opportunity for studying human evolution in action.

MOURANT: Our next speaker is Dr. Kalmus, who will discuss "Selection, Migration, and Drift."

H. KALMUS

Selection, Migration, and Drift

In population genetics, as in many other disciplines, the present may be considered in some ways as the remains of the past. Coming, as I just do, from the contemplation of the Palace of Knossos, I am acutely aware of my deficiencies in grasping historical contexts. When I consider any such remains, I do not know what is fact and what is fancy. Even if I do not doubt the authenticity of certain findings, I usually wonder whether their arrangement is original or due to later interference. Usually I am so bewildered by the richness and strangeness of the material that I find it difficult to connect it with any other historical epoch. I gather that both these embarrassments are at present shared by the experts.

In our own field, population genetics, the consideration of fact resolves itself into a critical examination of method. I do not want to enlarge upon the faulty techniques of the early blood groupers but will only quote two examples from my own experience. Several years ago, when planning to compare the frequencies of defective color vision in various populations, I referred to the literature and also applied to various governments and institutions all over the world. It soon turned out that owing to a multiplicity of methods—often inexpertly used—the data obtained were just fancy. For instance, I vividly remember the data pertaining to color blindness among the recruits in very remote regions of a certain country. Although annual population changes of large dimensions are most unlikely there, the frequencies of the various types of color blindness showed extraordinary variation from year to year and it was quite clear to me that these bizarre results were the product of very perfunctory examinations.

Similarly when, many years ago, Harris and I[1] applied Fisher's tea-tasting design to the determination of PTC thresholds of individuals previously tested with one or the other primitive method, we found on retesting that up to 8 percent of these persons had originally been misclassified.

It is clear that such results cannot form the basis for any valid speculation concerning migration, drift, or selection. But I should like to point out that the classical sex-linked forms of color blindness as well as PTC thresholds are exceedingly stable characters and that the fault lies with the investigators who would gladly devote a great deal of time and care to laboratory work but cannot be bothered to learn the methods of "exact subjectivism" and the statistics necessary for sense physiology.

Although the deficiencies of technique can be overcome—and it is one of the purposes of this conference to assist in the selection and standardization of techniques—it is not clear to me how the more fundamental difficulties of interpretation in population genetics can be resolved. This applies in particular to the history of gene frequencies in populations. To me the main difficulty is the fact that we do not know the frequency of any of our more common genes in any ancient population. We are thus compelled, when speculating, to explain a particular gene frequency in a living population in terms of hypothetical frequencies of its presumed ancestral group or groups—a process which involves a great deal of circular reasoning. On the whole I think that such speculations—especially if unsupported by evidence of a historical or other nongenetic nature—are of little value.

Moreover, the gene frequencies in related groups are amenable to two diametrically opposed interpretations. One can assume that the characters considered are selectively neutral, so that their frequencies in existent mixed populations can result from simple mixture of ancestral groups which in turn are assumed to be

1 Harris, H., and Kalmus, H., The measurement of taste sensitivity to phenylthiourea (P.T.C.), *Ann. Eug., 15,* 1950, 24–45.

genetically identical with their modern "pure" progeny. How, in the absence of differences in fitness, these original groups came to differ in their gene frequencies in the first instance is not clear—perhaps by drift.

On the other extreme one can consider certain characters in a population to be of strong selective significance and the genes determining them at any moment as subject to powerful selective forces. In such dynamic and often rapidly changing situations, the historical interpretation is very difficult and cannot be based on the consideration of static mixing. In particular, migration may, from this point of view, involve radical changes in the selective forces.

It is reasonable to suppose that fairly neutral genetic characters—if perhaps not quite neutral ones—coexist in any population with characters greatly affecting fitness. And in fact we can very often guess which are which. However, for a quantitative assessment of the carrier fitness for any of these characters we should require precisely the kind of historical information which we lack and which we want to infer in historical genetics.

These considerations, in my opinion, do not constitute an objection to the organization of our present meeting at this time and place. The ingathering of so many formerly separated groups of Jews certainly provides an opportunity for retrospective speculations of the rather dubious kind just described. More important, however, is the chance that by the full genetic investigation of the present immigrant groups we can provide real ancestral data for the future study of the effects of mixture, selection, and immigration in the population of this country.

MOURANT: Thank you, Dr. Kalmus, for your interesting contribution. Dr. Cavalli-Sforza will now present his paper, "Genetic Drift for Blood Groups."

L. L. CAVALLI-SFORZA

Genetic Drift for Blood Groups

I shall give a brief report of a research program which is now in its final stages and which was one by-product of an investigation of demographic material for genetic purposes. An area of the Parma province was chosen for this investigation, and the available parish books were copied and transferred to punched cards. Because the demography of the area for the last three centuries would thus become known, it was thought that a survey of blood groups and other traits of the inhabitants might make an interesting addition to the program. Although the demographic analysis is still incomplete, the blood survey of the Parma valley has been completed, about 75 villages (virtually all of the existing ones) having been

sampled (on the basis of approximately 40 individuals per village) and assayed for the ABO (4 sera), MN (2 sera), and Rh (5 or 6 sera) blood-group systems.

The 75 villages are grouped in 9 administrative units called *comuni*. It is important to note that some of these are in the mountainous region of the Parma valley, some in an intermediate hilly region, and some in the plains region nearest to the town of Parma.

An assay of differences in blood groups among the subareas—*i.e.*, the *comuni*—shows a heterogeneity when tested by χ^2. Most of the χ^2 values shown in Table I are significant. Various groupings of the phenotypic classes have been tried in order to avoid the possible vagaries of χ^2 when class frequencies are too small.

TABLE I

HETEROGENEITY FOR BLOOD GROUPS IN THE PARMA VALLEY

Groups	*Pooling of phenotypic classes*	*Between comuni* χ^2	df	χ^2/df	*Within comuni* χ^2	df	χ^2/df	$F = \frac{\chi^2/df\ (between)}{\chi^2/df\ (within)}$
ABO	none pooled	64.54	40	1.613				
	A_1B + A_2B pooled	50.67	32	1.583	425.82	260	1.638	1/1.035 not sig.
	A_2 + above ,,	33.79	24	1.408	314.09	195	1.611	1/1.44 ,, ,,
	B + above ,,	25.06	16	1.566	277.99	130	1.754	1/1.20 ,, ,,
MN	none pooled	28.67	16	1.792	227.93	130	1.753	1.022 ,, ,,
Rh	8 classes	107.43	56	1.918				
	7 classes	100.05	48	2.084				
	6 classes	80.99	40	2.025	484.47	325	1.419	1.358 ,, ,,

It will be seen that the pooling has virtually no effect; the ratio χ^2/df remains almost constant. Because the χ^2 among the subareas is often significant, one might conclude that the area, even though small, is heterogeneous for the three blood-group systems. That this is not so, however, is shown by the rest of the table. Also, the χ^2 values among the villages belonging to the same *comuni* (*i.e.*, "within *comuni*") are highly significant and show a "microheterogeneity" which should be noted when the homogeneity of the whole area is being examined. An analysis of variance, even if approximate, is a suitable test in this case. This analysis, summarized in the last column of the table, shows that no heterogeneity is detectable by this criterion in the entire area.

When the heterogeneity for the three blood-group systems is tested for the single *comuni*, a clear-cut picture is found. All significant χ^2s are in the mountainous region, and almost all χ^2s are significant there, whereas none is significant in the plains region. In order to make χ^2 values for different blood groups and different areas more easily comparable, χ^2 was divided by its degrees of freedom. If the number of degrees of freedom is high, this quantity is almost equal to 1 provided there is no deviation from random sampling. It will be higher than 1 in the presence of "drift" or other causes of variation among villages. The square root of χ^2/df is almost normally distributed with known standard deviation, and its excess above 1 has been used in Figure 7 as an approximate measurement of drift (or, more

exactly, the variation not accounted for by random sampling). In this figure, drift thus measured is plotted against population density, an important demographic variable, as we shall see, and the χ^2 values are pooled over the three blood-group systems. The result is that significant drift is observed in only the lower-density *comuni* and not in the higher-density *comuni*.

In implicating drift as the major cause of the heterogeneity observed, we are, of course, confronted with the limitation that we cannot accept this explanation before eliminating other possible causes, such as historical accidents or geographic heterogeneity in selective conditions. There is no trace of the former in this area. The only immigration known to have occurred in historic times was a minor

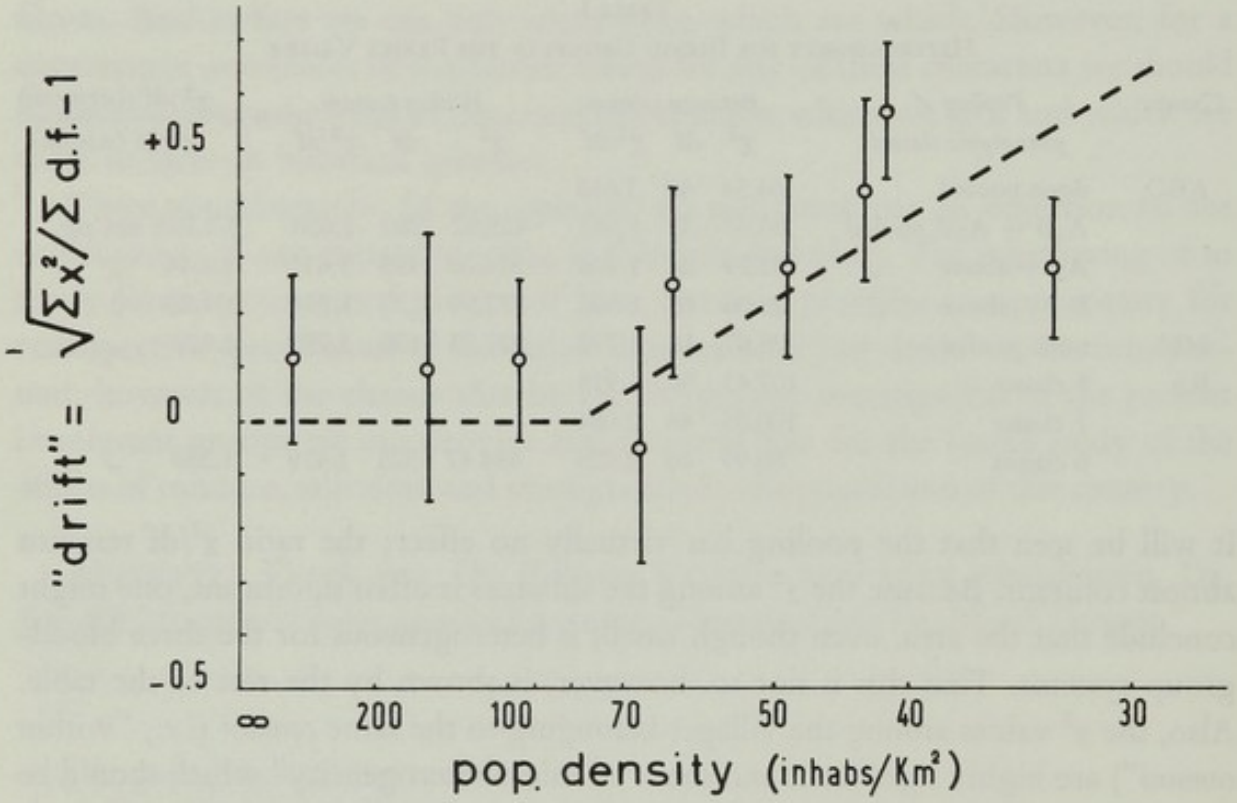


FIG. 7. The correlation between a measurement of "drift" for blood groups in 9 *comuni* of the Parma valley and their present population density.

settlement, which probably took place during the Seventh Century. All existing villages are known to have existed at least since the Eleventh Century, and no major changes in population figures have occurred during the past three centuries—*i.e.*, the period for which demographic data are available.

Another cause of variation which might be confused with drift—namely, local variation in selective conditions—is more difficult to detect or to exclude. At any rate, a test of Hardy-Weinberg equilibria in single villages showed no heterogeneity among villages for any of the blood-group genes tested.

It is also possible to test more directly the hypothesis that the observed heterogeneity found among villages is due to drift. This is done by checking whether the amount of variation observed corresponds to the amount expected on the

assumption that drift—*i.e.*, the accumulation over generations of random fluctuations in gene frequencies—is the sole cause of variation. The comparison between the observed and the expected amount of drift is made possible in this case by the demographic information available for the area. There are, however, two difficulties. First, the demographic investigation has not yet been completed, especially with regard to cross-migration among the villages. Secondly, the available models for predicting the expected amount of drift are often unsatisfactory when applied to real situations.

I shall report, however, on an analysis of the correlations between the observed amount of drift and the data available thus far on demographic variables, even though this cannot be completed until all the demographic data are assembled. In order to test the amount of drift expected in a population similar to the one being investigated, we have begun to set up, in an Olivetti computer, an artificial population which has the same demographic characteristics as that of the area being studied. This approach needs more work, and only the results of the correlation analysis will be presented here.

The following are the demographic factors that may be correlated with the observed amount of drift:

1. Population density. This varies from 30 to more than 300 inhabitants per square kilometer in the area studied.

2. Village size. This varies from 100 to more than 10,000 inhabitants.

3. Migration. We know that the percentage of people marrying in the same village varies from 30 to 80 percent in the area studied.[1] Unfortunately, we do not yet have complete estimates of migration, and therefore we did not consider it at this stage. Since we know, however, that other variables are highly correlated with migration, we have used them as temporary substitutes for migration. One of them is altitude; the other is mean consanguinity (calculated as α).

4. "Dimensionality." It has been shown[2] that a population spread in a unidimensional way is bound to produce more drift than one which has a bidimensional distribution. The mountainous areas are populated in an almost unidimensional way. A measurement of dimensionality was introduced by dividing the number of inhabitants living within a road distance of 10 km. from the village by twice the number of inhabitants living within 5 km. of the village.[3] This coefficient is 1 for a perfectly unidimensional distribution and 2 for bidimensional distributions. It can easily be calculated for each village. The arbitrary choice of 10 km. turned out to be the most satisfactory among various choices.

Finally, drift had to be estimated for each village. It was convenient to use χ^2

1 Cavalli-Sforza, L. L., Some data on the genetic structure of human populations, Tenth International Congress of Genetics, *Darwin Centennial Symposium on Genetics in Evolution*, *1*, 1958, 388–407.
2 Wright, S., The genetical structure of populations, *Ann. Eug.*, *15*, 1951, 323–354.
3 Cavalli-Sforza, L. L., and Conterio, F., Analisi della fluttuazione de frequenze geniche nella popolazione della Val di Parma, *Atti. V Riun. Scient. A.G.I.*, 1959, 1–11.

for the blood-group frequencies of a given village and the pooled blood-group frequencies of all villages within a distance of 10 km. from the given village. The χ^2 values for various blood-group systems were added together.

In an earlier paper, which analyzed the first half of these data,[4] another measurement (cos θ)[5] was used for the same purpose. In the present analysis, χ^2 was used because it was more easily calculated with the available facilities. For the purposes of correlation analysis, log χ^2 was used as the actual variable, because it was very nearly normally distributed. Other variables were given the same or another transformation in order to normalize the distributions and linearize the correlations. I must add that the use of the term "drift" assumes the still unproved hypothesis that drift alone is responsible for the observed heterogeneity.

The correlation coefficients calculated between drift and the variables defining the population are given in Table II. It will be seen that only the correlations with

TABLE II
ZERO AND HIGHER ORDER CORRELATION COEFFICIENTS BETWEEN DRIFT AND DEMOGRAPHIC VARIABLES

Correlation between drift and	*Zero order*	*Partial correlation coefficients after elimination of sample size and of:*					
		nothing else	*population density*	*village size*	*dimensionality*	*consanguinity*	*altitude*
population density	−.231*	−.212	—	−.159	−.211	−.139	+.065
village size	−.130	−.155	−.063	—	−.156	−.094	+.024
dimensionality	+.020	+.021	−.009	−.026	—	.000	−.023
consanguinity	+.191	+.162	.000	+.105	+.161	—	−.174
altitude	+.317†	+.310†	+.240†	+.273†	+.311†	+.339†	—
sample size	+.205						

* Significant at 5% level.
† Significant at 1% level.

population density and altitude are significant and that only the latter remains significant after elimination of the others. It is presumed that "altitude" reflects the migration pattern, and only when analysis of the latter is complete will it perhaps be possible to obtain a more satisfactory picture.

Dimensionality, at least as measured here, was found to play no role. Consanguinity was found to be a poor indicator of isolation, at least if drift, as measured, reflects isolation exclusively. Village size showed virtually no effect, at least as soon as the effect of the more important variables was removed. It is possible that a

4 *Ibid.*

5 Cos θ is a measure of similarity among gene frequencies for alleles 1, 2, 3, $\cdots k$ of populations A and B:

$$p_{1A}, p_{2A}, p_{3A} \cdots p_{kA}$$
$$p_{1B}, p_{2B}, p_{3B} \cdots p_{kB}$$

such that

$$\cos\theta = \sum_{i=1}^{k} \sqrt{p_{iA} p_{iB}}$$

For further information see footnote 3.

"continuous distribution" model using population density and migration as parameters, in the way suggested by S. Wright,[6] may eventually be found useful to represent this population, even if it is distributed in closely packed clusters, at least in that part of the area in which drift, if any, is observed.

MOURANT: Thank you. We now go on to the general discussion of all these papers. Prof. Heller?

HELLER: Familial Mediterranean Fever (described also under the names of Familial Recurrent Polyserositis, Epanalapsie Mediterranéenne, Armenians' Disease, Periodic Disease) has been known and studied as a nosological entity for less than a decade. It is an autosomal recessive disorder[1] obeying the Mendelian laws of inheritance and is characterized by fever and painful attacks in various locations, such as abdomen, chest and joints. Once the attacks have started, they will recur at irregular intervals throughout life. During the first three or four decades of life, one-third and probably more of the affected succumb to a rather characteristic amyloidosis.[2] Sometimes the amyloidosis precedes the attacks or remains the only manifestations of the disorder (see also pp. 286-289).

It is obvious that, through the complication with amyloidosis, FMF has a deleterious effect on survival and fertility of the affected homozygotes. No heterozygote advantage is apparent. The presumed biochemical error of metabolism has not as yet been discovered.

FMF shows a remarkable ethnic distribution.[3] In Israel, among 1 million Ashkenazim only 6 cases were observed, whereas among the 750,000 members of communities originating from the wider Mediterranean area, including Spain, North Africa, Israel, Syria, Iraq, Kurdistan, Turkey, the Balkans, and Greece, 350-odd cases have occurred. No case has been seen among Yemenite and Persian Jews. Allowing for inbreeding and late onset, the gene frequency of FMF among the Mediterranean group was estimated at 0.02 to 0.025, and among the Ashkenazim at 0.0024. Data from the literature confirm the prevalence of FMF among the Mediterranean Jews and illustrate, besides, the fact that the Armenian people is the second largest ethnic group affected (Table I). No difference between the Jewish and Armenian phenotype of FMF has been detected. Information is not sufficient for the estimation of the FMF gene frequency among Armenians. By virtue of its specific prevalence among Mediterranean Jews and Armenians, FMF may become useful as a genetic marker.

The observed facts pose some interesting questions to the population geneticist. Here are some of them: How is the difference in FMF gene frequency between the

6 *Loc. cit.*

1 Sohar, E., Pras s,M., Heller, J., and Heller, H., Genetics of Familial Mediterranean Fever (FMF), *Arch. Intern. Med.*, *107*, 1961, 529.

2 Heller, H., Sohar, E., Gafni, J., and Heller, J., Amyloidosis in Familial Mediterranean Fever, *Arch. Intern. Med.*, *107*, 1961, 539.

3 Heller, H., Sohar, E., and Sherf, L., Familial Mediterranean Fever, *Arch. Intern. Med.*, *102*, 1958, 50 .

Jewish ethnic subgroups to be interpreted? Is it possible that in the time available—that is, during 70 generations—genetic evolutionary forces such as inbreeding, genetic drift, and selection could have brought about such large differences? Or, alternatively, do we have to conclude that other factors, such as dilution with large numbers of genes from FMF-free ethnic groups must have been responsible for this differentiation?

TABLE I
ETHNIC DISTRIBUTION OF FMF CASES REPORTED IN THE LITERATURE

	Numbers	*Total numbers*	*Percent*	*Total percent*
Jews		133		51.6
Non-Ashkenazic Jews	117		45.3	
Jews—community not stated	16		6.2	
Non-Jews		125		48.4
Armenians	76		29.4	
Arabs	37		14.3	
Italians	2		0.8	
Turks	1		0.4	
Spaniards	1		0.4	
Not stated	8		3.1	
Total	258	258	99.9	100.0

What is the explanation of the selective occurrence of FMF among Armenians and Mediterranean Jews? Does it point to a common prehistoric origin for the two peoples? Or do we have here genetic evidence that, as a result of historical events about which the sources are silent or noninformative, large numbers of Mediterranean Jews have been admitted to the Armenian genetic pool?

We hope that future research will give an answer to some of these challenging questions.

ALLISON: I should like to ask Prof. Heller one question. I have heard it stated, or at least suggested, by some pathologists that Familial Mediterranean Fever might be connected with brucellosis because it is concentrated in certain sibships, or would tend to be, and the parents are unaffected, this being the chronic characterization of brucellosis. Of course, the difference between the Ashkenazim and the others could be explained on this basis, because the Ashkenazim may have a higher hygienic standard and do not drink goat's milk. I am sure that you in Israel are aware of this possibility and that you have excluded it, but I would like to hear your comments on this point.

HELLER: There is no evidence whatsoever for Familial Mediterranean Fever being connected with brucellosis. Familial Mediterranean Fever has been observed not only in Israel but also in America. Why should the Ashkenazic Jews in America be free of FMF while Mediterranean Jews or Armenians are affected? They

all live under the same environmental conditions. In North Africa only the Mediterranean Jews are affected, whereas the native Arabic-speaking people, living under the same conditions, are free of FMF.

ROBERTS: The present situation in Israel, in which a number of formerly discrete populations have now come together into a national polity, has given rise, as you all know, to what amounts almost to a laboratory situation for the analysis of evolutionary processes operating today in man. The question is how to set about that analysis.

It is not likely, I think, that you will be able to do anything in this country quite comparable to Dr. Cavalli-Sforza's sophisticated analysis of the Parma population. In his analysis, migration among communities with subsequent admixture occurs within a fairly homogeneous population and serves essentially to prevent local diversification of gene frequencies. Israeli groups are genetically much more heterogeneous, and intermixture is likely to bring about much more rapid and extensive changes in gene frequencies than selection or drift.

Now, it seems to me that some models of the effects of intermixture on gene frequencies recently investigated by Mr. Hiorns and me[1,2] may perhaps be of some use to workers in this field in this country. Intermixture rates can be determined easily and objectively; from them predictions can be made as to the course gene frequencies would follow if mixture were the only process modifying them; in future generations observed gene frequencies will be compared to these predictions. Any differences will indicate modification by selection or drift.

The dynamics of intermixture between two populations is susceptible to fairly elementary analysis. A variety of models can be set up for panmictic units if intermixture occurs at random. One may assume that generations are discrete, with intermixture only at the end of each, or one may assume that migration is continuous during generations. One may assume that migration rates are constant from generation to generation or vary either regularly or irregularly. I do not want to stress the actual formulas here. All I want to point out is that, when two populations are intermixing, it is possible to predict, on the basis of fairly simple equations, how the gene frequencies will change.

When, however, there are, as in Israel, more than two populations intermixing, exchanging genes, then the course their gene frequencies will follow cannot be written down in the form of equations, but the solutions can be obtained through matrix algebra. To illustrate the procedure, consider three Nilotic populations of the southern Sudan, where observations were made on the incidence of intermarriages. First the migration rates from the donating populations to the receiving populations are set out in tabular form. That table of intermixture rates is then

1 Roberts, D. F., and Hiorns, R. W., Population mixture and gene frequency change, Proc. 2d International Conference of Human Genetics, Rome, 1961. In press.

2 Roberts, D. F., and Hiorns, R. W., The dynamics of racial intermixture, *Amer. J. Human Gen.*, 1962. In press.

considered as a matrix (**M**); present frequencies of a particular allele in the three populations are regarded as the vector $\mathbf{q}_o$. If intermixture rates remain constant, then the frequencies ($\mathbf{q}_n$) at a future generation (n) will be $\mathbf{q}_n = \mathbf{M}^n \mathbf{q}_o$.

Figure 8 shows the future frequencies of blood-group gene M in the Nilotic populations as predicted by this procedure. I should say again that the procedure is not dependent on constant intermixture rates but can be modified to take variations into account.

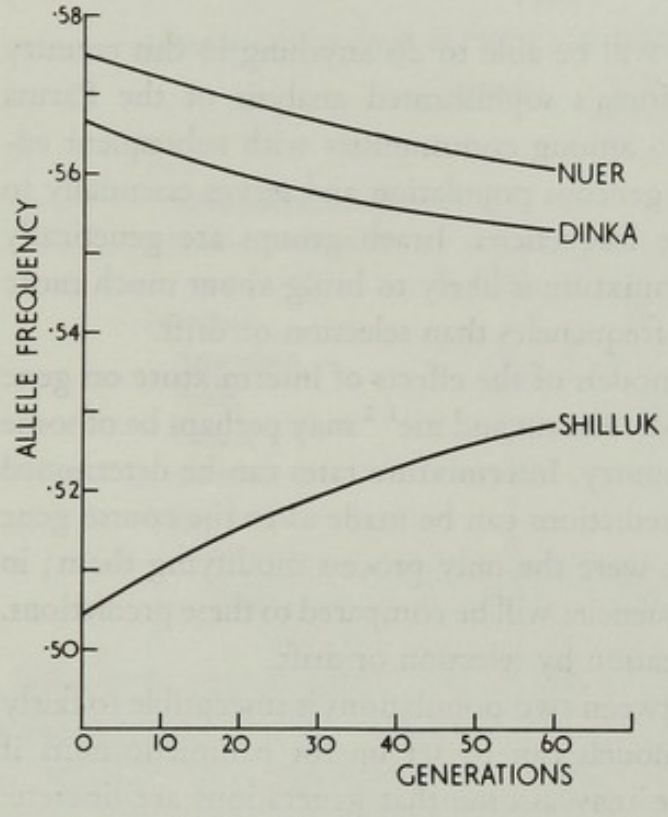


FIG. 8. Predicted approach through intermixture of frequencies of the gene for blood group M in the northern Nilotes.

NEEL: I should like to mention briefly some work on haptoglobin gene frequencies carried out by Dr. Ramot and Dr. Duvdevani at Tel Hashomer Hospital and by Dr. Sutton, Dr. Bayani-Sioson, and Mrs. Sandor of our group in collaboration with Dr. Goldschmidt, Dr. Fried, and Miss Bloch at the Hebrew University (see p. 266). Some 1600 serum samples, obtained from six principal groups—namely, Yemenite, Kurdish, Iraqi, North African, Sephardic, and Ashkenazic Jews—have been analyzed as to haptoglobin type. There is remarkably little variation in gene frequency among these communities, the frequency of the Hp^1 gene being rather close to .30 in all groups. The Sephardic Jews may show a somewhat higher Hp^1 frequency, .38.

There is a low frequency of the 2-1 modified phenotype. There is also a very low frequency of type O. The transferrins, which were studied at the same time, are all type C. There is apparent in the published material to date a rather striking north-south gradient in the frequency of the Hp^1 gene. The various Jewish groups that have been studied have been fairly well dispersed to both the north and the south; they fail to reflect this gradient.

This tends, I think, to underline one of the basic questions with which we will

be coming to grips. We have been reminded this morning of the many ways in which the Ashkenazic and non-Ashkenazic groups are known to diverge, not only in blood groups but also in erythrocyte defects and in FMF. One easy explanation is, of course, that these differences arose through intermarriage with local populations, but if we adopt that explanation, then we have to dispose in an intellectually satisfactory manner of the genetic traits for which there has been no divergence. Conversely, if we wish to emphasize genetic traits for which no diversity exists, then the riddle of the known genetic differences between non-Ashkenazim and Ashkenazim is intensified. One is forced to think about a relatively low rate of genetic exchange and perhaps a selective process which can result in a very rapid spread of certain genes throughout the genetic pool, once they have been introduced.

HALDANE: The data which have been presented have been of the greatest interest, and in particular it is most interesting to us to hear what is actually being done in Israel. I should like to make one plea. Human geneticists have to deal with apparently continuously varying characters. Most of them believe that human stature and similar quantitative characters are due, at least in part, to the interaction of numerous genes, each with a comparatively small effect. To judge from what we know, among those genes there may be some which can be detected by the various methods available. My plea is that in future work on any character—for example, on haptoglobin frequency—some attempt should be made to accumulate anthropometric data on the people concerned. It is perfectly clear that if that were done in Israel, one would get, at first sight, a quite spurious result. One would find that some blood groups, for example, were correlated with certain physical characters, because we know that both the physical characters and the blood-group frequencies vary in the different streams which are now coming together to make the new Israel. On the other hand, that criticism will not apply to differences between brothers or sisters. If, for example, a particular main haptoglobin gene were responsible for a change of 1 centimeter in height, on an average (and that is, of course, most unlikely), then we should find these differences on comparing members of the same family, and they would not be obscured by the environmental and genetic differences which we should find if we compared the people from different ethnic groups which are now coalescing.

I believe that, just because of the intensive character of the anthropometric studies which are being made in Israel, there is such a chance of observing pleiotropic effects of segregating alleles. They have been found, as we all know, by Italian workers in the case of Cooley's anemia or thalassemia, as it is called. That is, to my mind, a fundamental step in human genetics toward our aim of being able to specify at least some of the polygenes which are responsible for continuous variation.

I would therefore make a plea that the workers in this country who are doing such really fine work on various individual characters, studying the Mendelian

traits, should also study the continuous variation and particularly the differences between members of the same segregating family. There are wonderful possibilities in Israel which certainly do not exist in many other countries for following up individuals through at least some part of their lifetime. This may be a bee in my bonnet, but I am very strongly of the opinion that we are going to be able to identify some of these so-called polygenes by more striking effects, and it seems to me that Israel is a country where that may be done.

SHEBA: Some of the opinions voiced here concerning migration and drift are based on surveys concerned with only one or the other genetic marker. Conclusions should not be drawn prematurely. It might appear opportune to define a battery of markers essential for the purpose of studying evolution as proposed by Dr. Mourant.

If the frequencies of several marker genes are plotted against one another, we can hope to find an explanation for even the differences and the resemblances between Armenians and Mediterranean Jews.[1] FMF appears to be virtually restricted to these two groups so far as is known to us. On the other hand, Bauman and Walker[2] reported that among the Armenians available to them for study Glucose-6-Phosphate-Dehydrogenase deficiency was completely absent. If the past existence of a gene pool common to Mediterranean Jews and Armenians could be demonstrated by one genetic marker—namely, FMF—we should have expected to find a high incidence of G6PD deficiency in Armenians as well as in Mediterrancan Jews. However, unless one studies the origins of those Armenians who were screened for G6PD, one cannot arrive at conclusions. The distribution of the gene for the enzyme deficiency among Armenians may be as heterogeneous as among Jews from Kurdistan, where certain villages had an enormous incidence of enzyme deficiency whereas others had much less (see pp. 71 and 271).

We should also take into account Dr. Kalmus' remark that incorrect data may be produced by faulty technique or, when we use biochemistry as a tool, through the poor quality of the reagents. I would therefore suggest a "bureau of standards" for techniques and materials available to all of us working in the field. We could thus furnish reliable raw material, concerning 8 to 10 parameters, to the mathematicians, who would plot these data and offer their interpretation. Historians and mathematicians jointly might help us arrive at sound conclusions. Unaided by them, we should not attempt to infer too much from the study of only one or the other parameter.

MOURANT: Dr. Sheba has raised two very important points. The first is that of standardization of methods and reagents. This is a matter which is coming to the fore. I hope there will be discussions about this on a more worldwide scale at the International Conference of Human Genetics at Rome. It is a matter, at least as

1 Heller, H., Sohar, E., and Sherf, L., Familial Mediterranean Fever, *Arch. Int. Med., 102,* 1958, 50.
2 Bowman, I. E., and Walker, D. G., Virtual absence of Glutathione instability of the erythrocytes among Armenians in Iran, *Nature, 191,* 1961, 221-222.

far as serological reagents are involved, which is very much the concern at the moment of the World Health Organization (and, incidentally, of the Council of Europe) and is under active discussion.

The second point concerns the involvement of natural selection in determining the frequencies of alleles in the various polymorphic systems studied. As a practical proposition it is very important that we should try to make estimates of the relative degree to which natural selection and drift may have affected the relatively simple results that can be expected from the mixing of populations.

Since Dr. Morton has made such important contributions to the question of natural selection in human populations, I will ask him to add a few words to this discussion.

MORTON: Dr. Mourant referred to some preliminary work that has been done on the ABO and MN blood groups. The evidence that the MN blood groups are strongly influenced by selection goes back a long time to Taylor and Prior.[1] Already from the distribution of the genes, selection could have been inferred, because the gene frequencies are rather stable and gene M is a little more frequent than N. There are some exceptional populations in which appreciable deviation from equality may be observed, but the uniformity of the MN gene frequencies is rather impressive and strongly suggests that the polymorphism may be maintained by selection. Taylor and Prior[2] drew attention to an excess of heterozygotes in segregating families, and they were unable to find any technical error that would explain this. Wiener questioned this aspect of technical errors. Prof. Haldane, in his brilliant Croonian lecture, evaluated the MN material and concluded that technical error seemed unlikely to explain the MN excess. The debate continued. Race and Sanger, in their first edition, favored the idea of heterozygote advantage, but in the second edition they withdrew from this position.

Some time ago Dr. Chung and I began a preliminary study of some of the old data,[3] and this work was continued in collaboration with Dr. Matsunaga in Japan. In the material we analyzed there appeared to be a definite excess of MN. This excess was limited to matings in which the mother was type MN, and it was in several respects inconsistent with technical errors. I think these results are only preliminary, but they tend to underline the strong likelihood that the MN system is maintained by rather intense selection.

As for the ABO blood groups, we know that maternal-fetal incompatibility is an important aspect. Curiously, hemolytic disease of the newborn appears to be a rather special and perhaps minor facet of this problem.[4] The major effect of selection involves fetal loss not recognized as hemolytic disease of the newborn and

1 Taylor, G. L., and Prior, A. M., Blood groups in England. III. Discussion of the family material, *Ann. Eug.*, 1939, 18–44.
2 *Ibid.*
3 Morton, N. E., and Chung, C. S., Are the MN blood groups maintained by selection? *Amer. J. Human Gen.*, *11*, 1959, 237-251.
4 Chung, C. S., and Morton, N. E., Selection at the ABO locus, *Amer. J. Human Gen.*, *13*, 1961, 9-27.

distributed in a quite different way. Hemolytic disease of the newborn due to ABO incompatibility is restricted to children of type A or B, born to O mothers, whereas the abortion problem is definitely not so restricted and is distributed among all the ABO incompatible types.

Secondly, we found in family material from Europe and Japan a suggestion of heterozygote advantage in incompatible matings and also a suggestion that this increased with birth order. Again, this is quite a preliminary finding.

Recently, Matsunaga and Hiraizumi, in a report presented at the Pacific Science Congress in Honolulu and not yet published, have felt that they can demonstrate "meiotic drive" in the ABO system. This is a primary disturbance in segregation frequency acting before fertilization and, curiously enough, present in AO and BO fathers. They feel that the AO and BO males produce about 55 percent of O gametes. This is a little surprising because it tends to increase the frequency of O genes. The evidence is rather complex because we know of other selective mechanisms—namely, ABO incompatibility and possibly heterozygote advantage—and I am not convinced at this point that their claim is correct. But it does raise an extremely interesting possibility.

I think that all of this evidence, although of a highly preliminary nature, would support the contention of Dr. Kalmus and Dr. Neel and others that we should hesitate to infer admixture very far in the past from these blood-group systems.

MOURANT: Thank you, Dr. Morton. I am afraid that your suggestions about evolution have undermined a great deal of work that I have done in the past, but they must certainly be considered very seriously. I am still not entirely convinced in the case of MN, because I have personally come across so many cases of technical errors in these groups. I realize that you looked for them. You took this into consideration in your analysis, but certainly, in assessing any new data on MN, one must keep an open mind.

KALMUS: I should like to address a question to Dr. Morton. You mentioned Dr. Matsunaga's evidence on meiotic drive for the ABO system in Japan. It is not clear to me how Dr. Matsunaga was able to distinguish between meiotic drive and gametic selection.

MORTON: Several years ago Dr. Gullbring[5] reported that he had been able to separate A and B sperm of an AB male. A number of people have tried to repeat this and have failed and have not published their experiments. I know of several such attempts to repeat this work which have not succeeded. If such separation is possible, and it may well be, it would be extremely important, because Gershowitz *et al.*[6] have shown the existence of anti-A and anti-B activity in uterine secretions. However, if sperm express the phenotype of the male who produced them, then selection on the basis of the haploid genotype would not be possible. This is a

5 Gullbring, B., Investigation on the occurrence of blood-group antigens in spermatozoa from man, and serological demonstration of the segregation of characters, *Acta med. Scand., 159,* 1957, 169-171.

6 Gershowitz, H., Behrman, S. J., and Neel J. V., Hemagglutinins in uterine secretions, *Science, 128,* 1958, 719-720.

point of primary importance which at present remains unsolved and involves perhaps a higher order of immunological technique than has thus far been brought to bear on the question.

NEEL: With reference to this matter of gametic selection and the ABO groups—the work that Dr. Morton mentioned from Ann Arbor[1]—we originally looked into this because we were not satisfied by the medical evidence for the high fetal loss that must be postulated if this is what explains the abnormal genetic ratios. It would be well if the people who have made the negative observations on sperm dimorphism would publish their data. This is an extremely critical point. However, I am not sure the argument rests entirely on that observation, because if the A and B antigens are, for instance, in the prostatic secretions and can be secondarily absorbed in the sperm, then there is a mechanism for gametic selection, although it should involve total fertility rather than a disturbance of genetic ratios.

I might say that the work on cervical secretions has now been extended considerably.[2] There is no doubt that normal women may possess the alpha and beta agglutinins in rather high titer in their uterine secretions; thus far it has not been possible to relate titer to the stage of the menstrual cycle, to age, or to a number of other variants.

MOTULSKY: I would like to plead for more collection of data on the following design, which might give more information on the relative role of gene flow vs. selection. Investigate a number of markers—let us call them 1, 2, 3, 4, 5, and more, the more the better—in a Jewish population of a given area—say from Germany—and at the same time measure the frequencies of these traits among the German population, stipulating a Jewish population that has lived for many generations in the same environment as the German population. If you establish differences between the two groups in one or several traits, these may be ascribed to ethnic origin. If the two groups will be found similar in other traits, this suggests that selective factors have acted on them in a common environment. For instance, fingerprints appear to show differences between the Germans and the German Jews (see p. 282), whereas the ABO groups show fewer differences. I wonder if this indicates that fingerprints are adaptively more neutral whereas the ABO blood groups are subject to selection. This design has some internal controls. It would teach us a lot about adaptive vs. neutral factors. Many of the data are not available but could be assembled and might yield some interesting conclusions.

BLUMBERG: I just want to make one comment on Dr. Motulsky's suggestion. We are in the process of studying an American Negro population in the state of Georgia and contrasting them with the American white population who live under very similar environmental conditions in the same county. We have had the opportunity in conjunction with several collaborators—including Dr. Steinberg—

1 Gershowitz, H., Behrman, S. J., and Neel, J. V., Hemagglutinins in uterine secretions, *Science, 128,* 1958, 719-720.

2 Solish, G. I., Gershowitz, H., and Behrman, S. J., The occurrence and titer of isohemagglutinins in the secretions of the human uterine cervix, *Proc. Soc. Exp. Biol. & Med.,* 1962. In press.

of studying a large number of polymorphic traits, and we hope that this study may provide the type of information for which Dr. Motulsky has stressed the need.

STEINBERG: This remark is also addressed to Dr. Motulsky. I think this design is fine, but I urge a word of caution based on the following experience. You may recall that some years ago Dr. Bentley Glass studied the frequency of various blood groups in the Dunker isolate in the United States. It was found that the MN blood groups in this population differed from those of the ancestral population from which these people were believed to have been derived. It varied in the direction of the MN frequency of American Indians. Subsequent to Dr. Glass's studies, I studied three small colonies of the large Hutterite group, on which I am still working, and found that the MN blood groups differed markedly from those of the population from which these people were believed to have been derived and tended in the direction of the American Indians.

I discussed these data with a distinguished evolutionist, who enthusiastically pointed out that we now had four indications of great selective value of the MN groups, since the variation in four instances was in the direction of those of the Indians. I collected some 16 other samples from the same population and the variation from the ancestral population was again marked, but it was in both directions, toward the Indians and away from the Indians. Hence, if you have one sample, you may draw rather incorrect conclusions, particularly if the samples come from isolates.

NEEL: I have only a minor comment on Dr. Motulsky's suggestion. There is a difficulty in knowing what is neutral. Anything as neutral as fingerprints might show their colors in due time.

SPURWAY: I should like to make another criticism of Dr. Motulsky's suggestion. I know of no reproductively separated communities living in the same countries that do not also have different customs, sometimes connected with food, sometimes not. These customs are not often common knowledge, though they are often used as part of the rationalization for the communities' remaining apart and having certain prejudices against one another. I do not think we know enough of these differences in environment that depend on tradition to appraise their importance.

I think the study suggested by Dr. Motulsky is both an investigation of those features of human environment which may have selective influences and of the relative susceptibility of gene frequencies to their impact. Such an investigation must therefore study two things which are interacting. It is not going to be a simple analysis.

STERN: Studies on polymorphism, significant though they are already, are still in an early stage. We are therefore not yet in a position to make full use of the exceptional opportunities provided by the various populations now living together in Israel. The genetic isolation of these populations will soon break down, presumably before the discovery of many new polymorphisms. Would it not be

advisable, therefore, immediately to begin storing large population samples of blood which may become useful 15 or 30 years later?

BLUMBERG: I should like to make some remarks about Dr. Stern's suggestion. Some two years ago we had a conference at the National Institutes of Health at Bethesda, Maryland. This question of preservation of samples was brought up and discussed. The World Health Organization is either in the process of doing so or has already established serum banks for the preservation of serum specimens for later use. The suggestion for organizing this bank came originally from people interested in studying the epidemiology of virus diseases. But the group of geneticists at Bethesda who studied this question also indicated the very important concern that human population geneticists have in this matter, and there is a continuing discussion of this problem in progress.

MOURANT: There is one difficulty in the way of preserving specimens. We can undoubtedly preserve serum specimens and, with rather greater difficulty, we can preserve erythrocytes, and even platelets. But maybe in a few years' time research will tend to concentrate on leukocyte polymorphism (see p. 264), and we do not know how to preserve those.

Any further discussion? If not, I would like to thank all the speakers who have contributed papers to this session and also those who have taken part in what has been a most interesting discussion.

SESSION 2 A. C. ALLISON, *Chairman*

ADAPTIVE VALUES OF ERYTHROCYTE DEFECTS AND THEIR CHANGE WITH ENVIRONMENTAL CONDITIONS

ALLISON: We have a long session before us. We have a lot of interesting things to discuss, and I think we should get off straight-away to the first part of the presentation, which will be by Dr. Lehmann. Today, instead of having a series of set papers, we plan to have a presentation by subject. We are going to begin with a series of discussions of the characters with which we are dealing, the different hemoglobin types and how one recognizes them—particularly the more difficult ones such as thalassemia—and also the variant forms of Glucose-6-Phosphate-Dehydrogenase deficiency, this information having come out quite recently. After this discussion of the characters themselves, we shall consider briefly their distribution, and then we shall see whether it is possible to explain this distribution in intelligible terms, first by discussing selection operating against these factors, then by considering selection operating in favor of them. Finally, we shall consider whether other factors apart from selection, such as migration and drift, need to be invoked to explain the distribution.

Dr. Lehmann is going to begin by discussing the definition of abnormal hemoglobins and thalassemia.

H. LEHMANN

Different Types of Hemoglobinopathy and Thalassemia

The discovery of the different polypeptide chains of human hemoglobin and the recognition that they are under independent genetic control have added greatly to our information on human genetics. The viability of gene carriers for mutant hemoglobins depends on the interplay between the physiological hemoglobins A and F—$\alpha_2\beta_2$ and $\alpha_2\gamma_2$. The fact that the β-chain production is relatively unimportant until the age of six months allows survival of homozygotes for abnormal β-chain genes *in utero*. Increased production of F and A_2 may modify the severity of the condition in later life. Alpha-chain abnormalities which must affect all three physiological hemoglobins—$\alpha_2\beta_2$, $\alpha_2\gamma_2$, and $\alpha_2\delta_2$—can be sustained only if they carry no gross disadvantage, and homozygotes for abnormal α-chain hemoglobins are at present not known. Recent evidence indicates that mutational changes are not restricted to the α and β chains but can occur in the γ and δ chains as well.

The thalassemias with which we shall be concerned in this session can also affect either the α chain or the β chain. Here again the pattern of distribution and the selective mechanism of β thalassemia resemble those of the hemoglobinopathies due to β-chain abnormalities. Whereas β-thalassemia homozygotes may live, α-thalassemia homozygotes are liable to die *in utero*. In Jews both β thalassemia and

α thalassemia have been found among non-Ashkenazim (see also p. 278). An intensive survey is indicated to clarify their incidence and to pinpoint the different groups in which these conditions occur. A study of their past history might throw light on the susceptibility of α and β thalassemia to natural selection.

ALLISON: We shall now ask Dr. Aksoy, who has done interesting work on the distribution of abnormal hemoglobins in Turkey, to discuss some problems associated with thalassemia in Turkey.

M. AKSOY

Studies on Thalassemia in Turkey

Various forms of hemoglobinopathies are widely distributed in Turkey. In this meeting, I want to mention only some of the types heterozygous for the thalassemia gene. The heterozygous manifestations of the thalassemia gene exhibit a wide spectrum of clinical and hematological severity, as has been stressed by several authors.[1-3] There are a number of types of thalassemia minor, ranging from asymptomatic thalassemia minima to very severe forms of thalassemia minor resembling the intermediate type of Cooley's anemia. Although these severe forms of thalassemia minor are similar with regard to the clinical and hematological findings, they differ markedly in fetal hemoglobin content. According to the amount of fetal hemoglobin, thalassemia minor can be divided into two main forms: (1) thalassemia minor with normal or slightly elevated fetal hemoglobin; and (2) thalassemia minor with large amounts of fetal hemoglobin.

To date, we have observed nine cases of thalassemia minor with large amounts of fetal hemoglobin in seven families.[4-6] Among the findings in these patients and their families, three features appeared very important to us:

1 Singer, K., Chernoff, A. I., and Singer, L., Studies on abnormal hemoglobins. I. Their demonstrations in sickle-cell anemia and other hematologic disorders by means of alkali denaturation, *Blood, 6,* 1951, 413–428.

2 Chernoff, A. I., The human hemoglobins in health and disease, *New Engl. J. Med., 253,* 1955, 322–331, 365–374, 416–423.

3 Zuelzer, W. W., Neel, J. V., and Robinson, A. R., Abnormal hemoglobins, *Prog. Hemat., 1,* 1956, 91–137.

4 Aksoy, M., Thalassaemia minor with a large amount of foetal haemoglobin (report of four cases), *Acta haemat., 22,* 1959, 188–193.

5 Aksoy, M., Eğribozlu, A., and Alpüstün, H., The thalassaemia syndromes. I. Thalassaemia minor with large amount of foetal haemoglobin. Study of a family, *Acta haemat., 25,* 1961, 136–142.

6 Aksoy, M., Thalassaemia syndromes. III. Genetic studies on thalassaemia minor with large amount of foetal haemoglobin. Report of two new families. (To be published shortly.)

1. The amount of fetal hemoglobin found in these nine cases was very high, ranging from 22.5 to 63 percent, as seen in thalassemia major.

2. Although there was permanent anemia of moderate or severe degree which had begun in childhood, the patients had been very seldom transfused. On the other hand, the hematological and clinical findings were very similar to those of an intermediate type of Cooley's anemia or of double heterozygous conditions.

3. According to the family studies, those patients were heterozygous for the thalassemia gene. Genetic studies were performed in six of these seven families. In four families only one of the parents was investigated. Hemoglobin A_2 content was found to be normal in two parents. Two parents who showed the mild stigmata of thalassemia minor had an Hb-A_2 level above normal. In two families genetic studies were performed in both parents. In each of these two families one parent showing the stigmata of the thalassemia gene was found to have also an increased Hb-A_2 content, whereas the other parent was entirely normal and possessed an Hb-A_2 level within normal limits.

To explain this unusual state of the heterozygous form of the thalassemia gene, several possibilities must be considered:

1. The patients exhibiting thalassemia minor with large amounts of fetal hemoglobin may manifest the interaction of the thalassemia gene with a gene for the persistence of fetal hemoglobin production (or the gene for Lepore hemoglobin). As a result of the family studies and of the hemoglobin analyses this possibility has been excluded.

2. The presence of one of several different genes may be responsible for the thalassemia syndrome. This possibility was also excluded because of the significant differences between the clinical and hematological pictures of the affected parent and the patient.

3. The parent who is apparently free from thalassemia may have a thalassemia-like gene which is also connected with the formation of hemoglobin. The interaction of this hypothetical gene with the thalassemia gene inherited from the other parent may result in a syndrome similar to the intermediate type of Cooley's anemia or to the double heterozygous thalassemia syndrome[7] as observed in our patients exhibiting thalassemia minor with large amounts of fetal hemoglobin.

The normal adult hemoglobin molecule is now known to be made up of two pairs of polypeptide chains, an α pair and a β pair. According to the hypothesis of Ingram and Stretton, there are two general types of thalassemia, α thalassemia, and β thalassemia.[8] Hunt showed that fetal hemoglobin consists of one pair of α and one pair of γ chains.[9] On the basis of these facts, the hypothetical thalassemia-like gene

7 Singer, K., Singer, L., and Goldberg, S. R., Studies on abnormal hemoglobins. XI. Sickle-cell-thalassemia disease in the Negro; the significance of the S + A + F and S + A patterns obtained by hemoglobin analysis, *Blood, 10,* 1955, 405–415.

8 Ingram, V. M., and Stretton, A. O. W., Genetic basis of the thalassaemia disease, *Nature, 184,* 1959, 1903–1909.

9 Hunt, J. A., Identity of the alpha-chains of adult and foetal human haemoglobin, *Nature, 183,* 1959, 1373–1375.

is responsible for a β-chain abnormality. The interaction of this hypothetical gene with the gene for β thalassemia results in a syndrome similar to the intermediate type of Cooley's anemia.

It is known that hemoglobin H appears only in individuals who are also affected with another genetic anomaly pertaining to hemoglobin formation. In the great majority of cases, hemoglobin H has been demonstrated in association with the thalassemia trait and in only one instance with an abnormal hemoglobin, hemoglobin Q.[10] We propose a similar pattern of inheritance for the hypothetical thalassemia-like gene.

4. Different combinations of environment and genetic modifiers are responsible for the various heterozygous manifestations of the thalassemia gene. This possibility has been proposed by several investigators in order to account for the wide spectrum of clinical and hematological pictures observed in the heterozygotes for the thalassemia gene. But the exact nature of these hypothetical modifiers has not been indicated.

On the other hand, we observed two patients[11] with thalassemia minor exhibiting only slightly elevated fetal hemoglobin (4 and 5 percent, respectively) but resembling in all other aspects the intermediate type of Cooley's anemia or thalassemia minor with large amounts of fetal hemoglobin. The only difference consisted in the amount of fetal hemoglobin, which was 5 percent or less.

For the explanation of this type of thalassemia syndrome we propose a thalassemia-like gene responsible for an α-chain abnormality. The interaction of this hypothetical gene with the β-thalassemia gene may result in a thalassemia syndrome resembling the intermediate type of Cooley's anemia or the above-mentioned form of the thalassemia syndrome except for the fetal hemoglobin amounting to less than 5 percent.

It will be obvious from the foregoing considerations that much more advanced genetic, hematological, and particularly biochemical investigations are required for a full explanation of the different heterozygous manifestations of the thalassemia gene.

ALLISON: Now we shall ask Dr. Fessas to summarize his experience with the different forms of thalassemia in Greece, and to give us some advice on the detection of these different forms, which is a very difficult technical problem.

10 Vella, F., Wells, R. H. C., Ager, J. A. M., and Lehmann, H., A haemoglobinopathy involving haemoglobin H and a new (Q) haemoglobin, *Brit. Med. J.*, *i*, 1958, 752-755.

11 Aksoy, M., Thalassaemia syndromes. IV. A severe form of thalassaemia minor with slightly elevated foetal haemoglobin. Study of a family. (To be published shortly.)

PH. FESSAS

Screening Methods in Population Studies of the Different Thalassemia Types

I certainly agree that the recognition of the thalassemia trait often presents a difficult technical problem, but I shall try to simplify this to some extent. You have already heard that there are probably many types of thalassemia. Now, how can these be distinguished?

It is rather unfortunate that all forms of thalassemia trait manifest themselves by very similar findings when examined by the classical hematological methods. This may be of importance to the population geneticist who wishes to establish the specific incidence of each type of abnormal trait. I should like to give a brief outline of some of the procedures which guarantee a fair amount of accuracy when applied in population screening.

The simplified osmotic fragility tests may be mentioned first. There are several modifications of these tests, and each laboratory has its own preference. They may all be satisfactory, but none of them is sufficiently accurate. In our experience, at all events, about 8 percent of thalassemia-trait carriers will be classed as normal when tested by one of these fragility screening tests. The exclusive application of such a test will therefore lead to the underestimation of the frequency of the thalassemia traits. However, it may also give rise to an overestimate if the sample of the population contains a large number of women or young children with iron deficiency, because such cases will exhibit increased osmotic resistance even though they may not possess the thalassemia trait.

The second method which is also very good for screening purposes is the evaluation of the morphology of the red cells. In our experience this is probably the best single method; it does not let us down except in approximately 1 to 2 percent of the cases. The disadvantage of this method is that it requires a considerable amount of experience; it is too "subjective" to be applied in any laboratory.

If we accept thalassemia as a quantitative defect of globin synthesis, then this defect should be reflected in the total amount of hemoglobin present in the red cell; such a hemoglobin deficit can be estimated by careful hemoglobin measurement in conjunction with the red-cell count. In our experience, the use of these two measurements and the calculation of the mean corpuscular hemoglobin (mμg per cell) is the most accurate of all the classical methods for ascertaining the presence of the thalassemia trait in a person and in a sample of the population. It should, however, be taken into consideration that iron deficiency, again, has to be

excluded. This is one difficulty, and another one is due to the well-known fact that red-cell enumeration is not always accurate. This shortcoming can be avoided by the use of an electronic cell counter, which is invaluable for large surveys. In our hands, at least, the combination of these two measurements offers the best results.

As I stated at the beginning, none of these tests can distinguish between the various types of thalassemia trait. This differentiation may be achieved by applying a battery of other methods. Table I lists the methods we have been using in the investigation of the Greek population. These methods, although not very difficult to apply, are sometimes too time-consuming in large-scale work. Following a careful screening of a sample of the population, and by the application of these methods, we have obtained the following classification of the types of thalassemia traits found in Greece:

TABLE I

METHODS USED FOR THE CLASSIFICATION OF THE THALASSEMIA SUBTYPES

1. Paper electrophoresis, *p*H 8.2.
2. Starch-block electrophoresis for quantitative determination of Hb A_2.
3. Alkali denaturation, 1-minute test, for quantitative determination of Hb F.
4. Starch-gel electrophoresis, *p*H 8.4, for small "slow" fractions.
5. Starch-gel electrophoresis, *p*H 6.8, for small "fast" fractions.
6. Test for inclusions of Hb.

An elevated hemoglobin A_2 is accepted as one of the best criteria for the diagnosis of the thalassemia trait, and, indeed, the type of trait presenting an increased A_2 fraction is the most frequent in our series. In addition, some of these cases may exhibit an elevated fetal hemoglobin; however, this finding is not generally obtained and its significance is still obscure.

The distinction between α-chain and β-chain thalassemia has already been mentioned during this session; in the α-chain variety the hemoglobin A_2 fraction should not be increased, whereas in β-chain thalassemia it should be elevated. However, there are exceptions to this rule: in some β-chain thalassemias we may not have an increase in hemoglobin A_2 but solely an elevation of hemoglobin F. Apparently an increased A_2 component is not a prerequisite for the diagnosis of all β-chain thalassemias. This finding is illustrated by the second group of cases, which constitutes approximately 10 percent of the thalassemia traits found in Greece and in which an elevated hemoglobin F, ranging from 5 to 15 percent, is found in the absence of an elevated hemoglobin A_2.

The small third group comprises cases presenting an abnormal hemoglobin, provisionally called hemoglobin "Pylos," possibly similar to hemoglobin "Lepore"; this group is included with the thalassemias in spite of the presence of an abnormal hemoglobin. For several reasons it should be considered as a β-chain thalassemia rather than an abnormal hemoglobin syndrome.

The fourth group, which comprises the α-chain thalassemias, deserves especial

attention. These traits are the most difficult to recognize. The existing information on this type of thalassemia derives almost exclusively from clinical material, and hardly any data from population studies are available.

The presence of an α thalassemia does not appreciably affect the ratios of the various hemoglobin fractions. Hence, diagnosis of this abnormality requires more refined methods. One method is the detection of very small amounts of β-chain tetramer (hemoglobin H) or of γ-chain tetramer ("fast" fetal fraction = hemoglobin "Bart's"); such detection is often difficult and does not lend itself to large-scale studies. A second method is the histochemical detection of the presence of hemoglobin H in the red cells. However, these typical hemoglobin H inclusion bodies may be found in extremely few red cells, often in only one out of 5 to 10

TABLE II

TYPES OF THALASSEMIA TRAITS AND THEIR RELATIVE INCIDENCE, IN PERCENT

1. Elevated Hb A_2, with or without elevated Hb F	78
2. Elevated Hb F, without increased Hb A_2	10
3. Presence of Hb "Pylos" (= Lepore?)	2
4. Hb H, or inclusions of Hb H and/or small amounts of the "fast" fetal fraction (= Hb "Bart's")	5.5
5. Absence of any demonstrable biochemical abnormality	4.5

thousand cells. It should be pointed out that not all α-chain thalassemias become manifest as overt hemoglobin H disease, either clinically or on hemoglobin analysis. In Greece, because of the low incidence, it is difficult to determine the exact ratio of overtly affected among the gene carriers. However, it appears that less than one tenth of the α-thalassemia trait heterozygotes present the biochemical picture of hemoglobin H disease.

Information on the frequency of α thalassemia can be obtained by examining cord-blood hemoglobin. The study of this material may yield the best estimate of the incidence of the trait in a given population. A small excess of γ chains, forming the "Bart's" tetramer, appears to exist in all cord bloods; in the presence of an α-chain thalassemia this excess is accentuated to a degree facilitating its detection by electrophoresis. Employing mainly electrophoresis on starch gels at a slightly acid *p*H, we have determined an incidence of Hb "Bart's" in 4 per 1000 of the Greek newborn; this figure agrees very well with independent estimates, obtained by the application of all available methods for the detection of α thalassemia in a study of adult samples. Now, this is a low incidence, but I feel certain that in other regions of the world the incidence of this type of thalassemia may be considerably higher. Areas such as Thailand and Indonesia, and more specifically their Chinese populations, could be successfully screened by the study of cord bloods.

Finally, I would like to present a few figures concerning the prevalence of the thalassemia traits in various parts of Greece, as obtained in a recent study[1]; the

[1] Malamos, B., Fessas, Ph., and Stamatoyanoopoulos, G., Types of thalassaemia trait carriers as revealed by a study of their incidence in Greece, *Brit. J. Haem.*, *8*, 1962, 5-14.

figures concern all types of traits. Although the most frequent type is the β-chain thalassemia presenting an elevated hemoglobin A_2, the total of all other types contributes a far from negligible fraction. Since it is highly probable that the relative incidence of these types in other parts of the world may be different from the one found in Greece, an approach to the thalassemias with the same attitude as the abnormal hemoglobins—*i.e.*, with the aim of specifying their types as accurately as possible—seems indicated.

TABLE III
PREVALENCE OF THALASSEMIA TRAIT IN AREAS OF GREECE, IN PERCENT

Peloponnese	6.3
Central Greece and Euboea	7.3
Thessaly	11.5
Epirus	12.2
Macedonia and Thrace	3.3
Ionian Islands	14.0
Aegean Islands, Crete, and Dodecanese	7.6

ALLISON: Dr. Motulsky has a few words to say on other genes that could give rise to the appearance of conditions very similar to thalassemia.

MOTULSKY: Following up Dr. Fessas' remark on the detection of α thalassemia in cord bloods, I should like to mention briefly some data on the incidence of this defect in eastern Asia. At a recent conference in Honolulu, Dr. Eng, from Indonesia, reported that among Chinese babies 3 to 5 percent of the cord bloods contain Hb Bart's, whereas among Malayans the incidence is slightly lower. Thus α thalassemia seems to be a very frequent trait in that part of the world. Also, in personal conversations with a hematologist in Honolulu, I was told that in the past 4 years he had seen 14 cases of hemoglobin H thalassemia, mostly in Chinese, again suggesting that the frequency of α thalassemia in Chinese is fairly high. Since this group also has a fairly high incidence of β thalassemia, this may be the only population in the world with an equal incidence of β and α thalassemia.

When discussing the genetic control of the functional hemoglobin molecule, we should keep in mind that in addition to the loci responsible for the production of the α and β polypeptide chains, the synthesis of the heme group starting with the synthesis of δ-amino-levulic acid and ending up with the incorporation of iron into the porphyrin ring requires a series of enzymes controlled by a series of genetic loci. In addition to these structural genes for heme-synthesizing enzymes and hemoglobin polypeptides, the existence of genes[1] promoting or suppressing the formation of different types of polypeptide chains has to be envisaged. An effort should be made to restrict the term "anemia" to those defects which alter the structure or the rates of synthesis of the various polypeptide chains in the globin molecules.

1 Motulsky, A. G., The "high fetal hemoglobin" gene: A clue for gene mapping at the human β-hemoglobin locus. Proceedings, Second International Conference on Human Genetics, 1961. In press.

ALLISON: Now we have discussed very briefly the types of defect we are dealing with, and Dr. Cabannes will give us an account of the geographic distribution of the abnormal hemoglobins with special reference to Algeria, where he himself has done so much work on these characters.

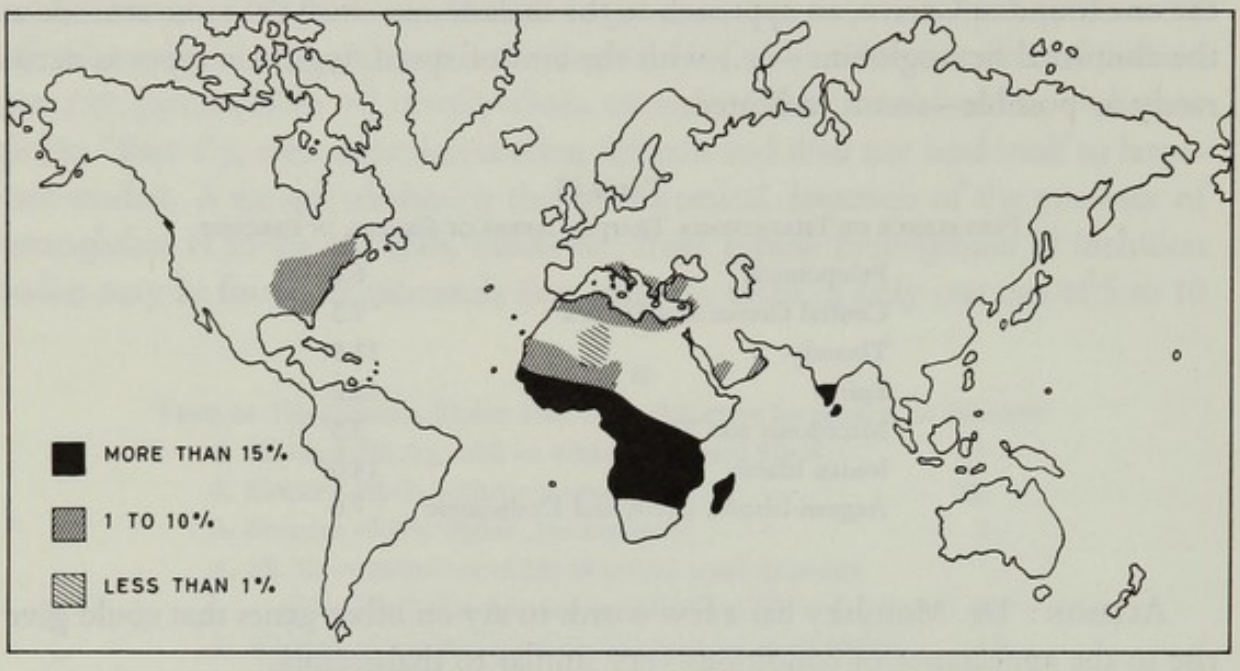


FIG. 9. World distribution of Hb S.

R. J. CABANNES

The Geographic Distribution of Hemoglobinopathies with Special Reference to the Mediterranean Region

THE ABNORMAL HEMOGLOBINS

The geographic distribution of the abnormal hemoglobins has by now been thoroughly mapped out. The population genetics of the more common among the inherited anemias, at any rate, has been dealt with in numerous investigations.

The distribution of Hb S, which has been most thoroughly studied, is indicated in Figure 9. The "sickle belt" of Central Africa, including Madagascar, is bounded on the north by a line extending from the mouth of the Senegal River to the southern border of Somaliland. The belt extends south to the Zambesi River. The population of this zone has a very high rate of sicklers, amounting to 25 percent on the average. But the sickle-cell gene is also widespread outside this zone. With the exception of France, sicklers exist in all countries bordering on the Mediterranean shores, and in the Middle East, on the Arabian Peninsula, in the Veddoid populations

of southern India, as well as in northern Thailand. A certain proportion of sicklers is also found among United States citizens and among Central and South Americans of African or partly African origin.

Wherever the sickle gene occurs in high frequencies it coexists with the malaria

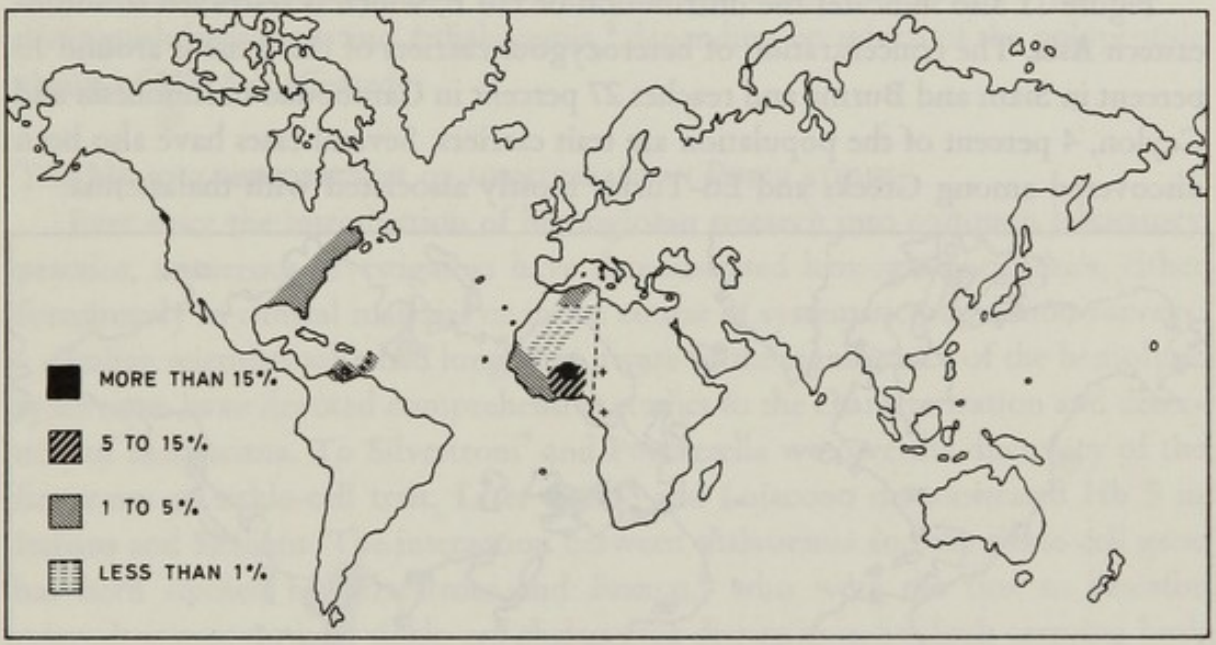


FIG. 10. World distribution of Hb C.

parasite, in the presence of which it is known to gain a selective advantage. The resulting interplay of opposed selective forces gives rise to a balanced polymorphism.

The hemoglobin C trait has also been thoroughly mapped (Fig. 10). It is now well established that the highest concentration of heterozygotes for the Hb C gene exists on the Volta Plateau in northern Ghana, as has been demonstrated by Lehmann and Edington,[1] as well as by Sansarricq *et al.*[2] Outside this region the frequency of the C gene falls off in all directions. Its total distribution is restricted to the West African zone extending from the Mediterranean to the Gulf of Guinea. It is completely absent east of an imaginary line connecting the Gulf of Gabes with the Niger Delta. The immigration of West Africans into several American countries (U.S.A., Venezuela, Curaçao, Surinam) resulted, of course, in the introduction of the gene into the New World.

In comparison with the S and C genes, hemoglobin D is both rarer and less homogeneous in distribution (Fig. 11). Its peak frequencies do not exceed 1 percent and are found among the Gujeratis and the Punjabs of northwest India. This aberrant hemoglobin is also found in Turkey among the Eti-Turks as well as

1 Edington, G. M., and Lehmann, H. A case of sickle-cell haemoglobin C disease and a survey of haemoglobin C incidence in West Africa, *Trans. Roy. Soc. Trop. Med. Hyg., 48,* 1954, 332-335.
2 Sansarricq, H., Marill, G., Portier, A., and Cabannes, R., Les hémoglobinopathies en Haute-Volta, *Sang, 30,* 1959, 503-511.

among North African Whites, in some Italians, and in African and U.S. Negroes. Biochemical studies[3, 4] have recently demonstrated the existence of different types of Hb D (Dα, Dβ, Dγ) which are probably independent in origin and geographic distribution.

Figure 11 also indicates the distribution of Hb E, which is restricted to southeastern Asia. The concentration of heterozygous carriers of this gene is around 13 percent in Siam and Burma and reaches 27 percent in Cambodia. In Indonesia and Ceylon, 4 percent of the population are trait carriers. Several cases have also been discovered among Greeks and Eti-Turks, mostly associated with thalassemia.

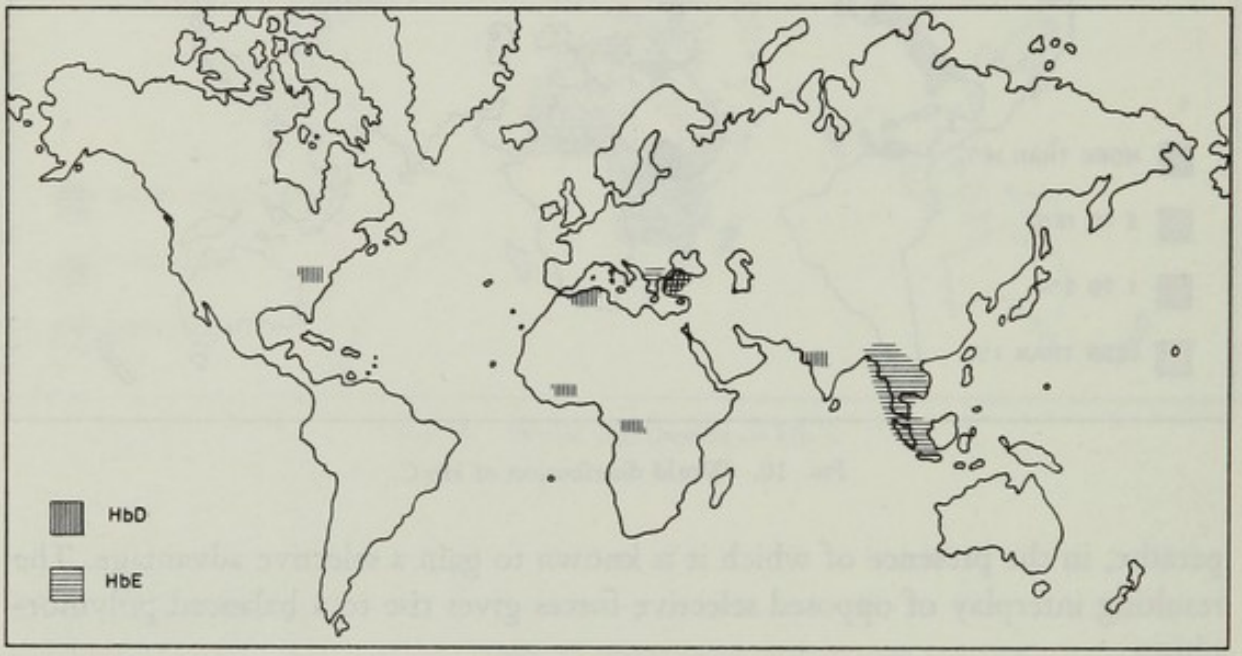


FIG. 11. World distribution of Hb D and Hb E.

A series of rare hemoglobins, including G, H, I, J, N, O, P, Q, R, Hb Stanleyville I and II, Hb Norfolk, and Hb Hopkins I and II, have been discovered in certain families dispersed throughout the world and devoid of any traceable connections. No anthropological interpretation has been offered for the erratic distribution of these rare hemoglobins.

A particular problem is posed by Hb K. It was first demonstrated in a Kabylic isolate of Algeria[5] and has also been found in Negroes, Indians, Malayans, and Sicilians. No conclusion can be drawn, as yet, from this scattered distribution.

THE THALASSEMIAS

The thalassemias do not belong to the abnormal hemoglobins in the narrow sense. Their distribution, however, overlaps to a large extent with that of the hemoglobinopathies proper. It is assumed that thalassemia is a disease which

3 Benzer, S., Ingram, V. M., and Lehmann, H., Three varieties of haemoglobin D, *Nature, 182,* 1958, 852-853.

4 Ingram, V. M., Constituents of human haemoglobins—separation of the peptide chains of human globin, *Nature, 183,* 1959, 1795-1798.

5 Cabannes, R., and Buhr, J. L., L'hémoglobine K. Identification, incidences biologiques et pathologiques, *Sang, 29,* 1958, 201-212.

prevails mainly in the poor and undernourished populations existing in certain areas of Italy, Greece, the Mediterranean Islands (Balearic Islands, Sicily, and Sardinia), North Africa, southeast Asia, and in the U.S. populations of Mediterranean, African, or Asian affiliation. The thalassemias frequently show familial association with the abnormal hemoglobins. Recently it has become possible to distinguish between α and β thalassemia,[6] depending on which of the polypeptide chains of Hb A is affected.

The Hemoglobinopathies of Mediterranean Populations

Ever since the introduction of hemoglobin research into common laboratory practice, numerous investigators have demonstrated hemoglobinopathies, either fortuitously in clinical material or in the course of systematic population surveys.

Italian scientists who had long been aware of the significance of the hemolytic syndromes have devoted comprehensive studies to the characterization and detection of thalassemia. To Silvestroni[7] and Purrazzella we owe the discovery of the first cases of sickle-cell trait. Later Gatto[8] and Lojacono demonstrated Hb S in Italians and Sicilians. The interaction between thalassemia and the sickle-cell gene has been studied by Silvestroni and Bianco,[9] who were the first to describe microdrepanocytosis or sickle-cell thalassemia disease in individuals carrying both the thalassemia trait and the sickle-cell trait. In the course of the past few years Silvestroni[10] and collaborators have discovered hemoglobins K and J, as well as D, G, L, P, and N, in southern Italian populations. Thus eight varieties of abnormal hemoglobins (S, D, G, J, K, L, N, P) are known to exist in Italy apart from the cases of Hb Bart's and Alexandra (Table I).

In Greece only three types of abnormal hemoglobins (S, H, and E) have been revealed thus far by various research groups,[11-13] in many of which Dr. Fessas was a prominent investigator. Apart from these abnormal adult hemoglobins, Fessas described two deviant fetal types, one being faster than Hb A,[14] the other, named "Alexandra,"[15] slower than Hb F in electrophoretic migration.

6 Neel, J. V., Genetic aspects of abnormal hemoglobins, NAS-NRC Conference on Hemoglobins' 1958, 253-271.

7 Silvestroni, E., and Bianco, I., Microdrepanocito-anemia in un suggetto di razza bianca, *Boll. Atti. Accad. Med. Roma, 69,* 1944, 1945, 293.

8 Gatto, I., and Russo, G., Risultati della nostre osservazioni sulla Drepanocitosi et Thalassodrepanocitosi, *Act. Gen. Med. Gemell., 8,* 1959, 179.

9 Silvestroni, E., and Bianco, I., Una nuova entità nosologica: la malattia micro-drepanocitica, *Haematologica, 29,* 1946, 455-488.

10 Silvestroni, E., Emoglobine abnormi et emoglobinopathie in Italia, *Policlinico Sez. Prat., 66,* 1959, 1373-1392.

11 Choremis, C., Ikin, E. W., Lehmann, H., Mourant, A. E., and Zannos, L., Sickle-cell trait and blood groups in Greece, *Lancet, ii,* 1953, 909-911.

12 Gouttas, A., Fessas, P., Tsevrenis, H., and Xefteri, E., Description d'une nouvelle variété d'anémie hémolytique congénitale; étude hématologique, électrophorétique et génétique, *Sang, 26,* 1955, 911-919.

13 Gouttas, A., Tsevrenis, H., Rombos, C., Papaspyrov, A., and Garidi, M., L'Hémoglobinose E en Grèce, *Sang, 31,* 1960, 1-5.

14 Fessas, P., and Papaspyrov, A., New "fast" hemoglobin associated with thalassemia, *Science, 126,* 1957, 1119.

15 Fessas, P., Mastrokalos, N., and Fostiropoulos, New variant of human foetal haemoglobin, *Nature, 183,* 1959, 30-32.

Since 1955 Turkey has been explored by Aksoy, who discovered Hb S in Turks and Eti-Turks.[16] He also demonstrated that Hb S in Turkish groups may occur either alone or associated with thalassemia or Hb E.[17] Moreover, Hb E, in turn, may occur singly or associated with thalassemia. Aksoy was also the first to demonstrate Hb D in Turkish populations.[18]

Only sporadic information has become available thus far concerning the Mediterranean coast of the Near East. However, Ramot and co-workers[19, 20] have discovered an Arab carrying a combination of Hb S and O with thalassemia, as well as the association of Hb H with Hb Bart's in an Oriental Jewish woman and her daughter (see also p. 278). Aksoy, on his part, found Hb S in the "Alléouites" of Lebanon.

TABLE I
ABNORMAL HEMOGLOBINS IN ITALY

Hemoglobin	*Number*	*Origin*
S	34	Sicily, Calabria, Latium
A_2 abundant	4	Po Delta, Calabria
H	6	Campania, Sicily, Emilia, Calabria
D	2	Calabria, Emilia
G	2	Emilia, Umbria
K	1	Sicily
J	1	Calabria
L	4	Emilia
P	1	Calabria
N	1	Sardinia
Bart's	5	Latium, Tuscany, Sardinia, Calabria
Alexandra	1	Latium

In Egypt and Libya, Lehmann has indicated the presence of Hb S. In autochthonous inhabitants of Tunisia, the sporadic occurrence of sickle-cell thalassemia disease has been detected in the course of family studies.[21]

More numerous and comprehensive investigations carried out in Algeria have resulted in the identification of six varieties of pathological hemoglobins. Follow-

16 Aksoy, M., Sickle-cell trait in South Turkey, *Lancet, i,* 1955, 589-590.
17 Aksoy, M., Bird, G. W. G., Lehmann, H., Mourant, A. E., Thein, H., and Wickremasinghe, R. L., Haemoglobin E in Asia, *J. Phys.* (London), *130,* 1955, 56.
18 Aksoy, M., and Lehmann, H., A further example of haemoglobin D in a Turkish family, *Trans. Roy. Soc. Trop. Med. Hyg., 50,* 1956, 178-179.
19 Ramot, B., Fisher, S., Remez, D., Schneerson, R., Kahane, D., Ager, J. A. M., and Lehmann, H., Haemoglobin O in an Arab family—sickle-cell haemoglobin O trait, *Brit. Med. J., ii,* 1960, 1228.
20 Ramot, B., Sheba, C., Fisher, S., Ager, J. A. M., and Lehmann, H., Haemoglobin H disease with persistent "Bart's" in an Oriental Jewess and her daughter. A dual alpha-chain deficiency of human haemoglobin, *Brit. Med. J., ii,* 1959, 1228-1230.
21 Roche, J., Derrien, Y., Diacono, G., Burieux, J., Laurent, G., Raymond, J., Roux, M., and Brangier, J., Coexistence des rares sicklémique et thalassémique dans une famille Tunisienne, *Rev. Hemat., 11,* 1956, 26-48.

ing the demonstration of Hb S and Hb C by Portier *et al.*,[22] Cabannes *et al.*[23] have identified D, J, K, as well as a curious association of A+D+K in a single subject. The combination of Hb S and Hb C is also known to occur, and Hb J has been reported in an autochthonous subject by Boulard, Cabannes, *et al.*[42]

The Jews of North Africa, whether they be allied to the Berbers or connected to the more remote Spanish or Slavic peoples, appear to be entirely devoid of hemoglobinopathies. At all events, our study of more than 150 Jews of Algeria has failed to reveal a single case of an abnormal hemoglobin or a thalassemia. No study has as yet been made of Moroccans except for the Sahara tribes in the Mauritanian area.

No hemoglobinopathies have thus far been reported from Spain. An indirect proof of the occurrence of Hb S may be derived from our observations of Hb S, C, and thalassemia in a young girl whose mother was of Spanish extraction and whose father was an American Negro.

Finally, from France only a single case of an autochthonous hemoglobinopathy has been reported. It is probably a new type of hemoglobin not yet represented in the accepted classification. No reference will be made to pathological hemoglobins described in French citizens of Oriental extraction.

In conclusion it may be stated that around the Mediterranean basin in populations which are quite diverse, although possibly connected by remote common roots, abnormal hemoglobins are by no means rare (see Fig. 12). At least 13 varieties are known to exist (S, D, C, E, H, I, J, K, L, O, Bart's, and two other abnormal fetal hemoglobins). Far from being mere anthropological curiosities, a number of these abnormal hemoglobins represent important pathological elements, since singly or in association with thalassemia they affect about 2 percent of Italian, Greek, and Algerian populations. In Algeria, where Hb C is the most common hemoglobinopathy, it occurs in 1½ to 2 percent of the autochthonous population.

Not all the manifestations of these hemoglobinopathies are morbid. Although some of them give rise to genuine disease with an impressive array of severe clinical symptoms, the majority remain inconspicuous in single dose. Nevertheless, they represent a latent danger because of their diffusion and their potential association with other genetic entities and the risk of their appearance in double dose.

ALLISON: From the point of view of population genetics, I think it is important to recognize that these hemoglobinopathies fall into two classes. One class com-

22 Portier, A., Cabannes, R., and Duzer, A., The frequency and distribution of abnormal haemoglobin conditions in Algeria, in J. H. P. Jonxis and J. F. Delafresnaye (eds.), *Abnormal Haemoglobins*, Blackwell, Oxford, 1959, 279-289.

23 Cabannes, R., Duzer, A., Portier, A., Massannat, J., Sendra, L., and Buhr, J. L., Hémoglobines anormales chez l'Algérien musulman, bilan statistique de deux années d'études portant sur 1877 hémoglobinogrammes, *Sang, 27,* 1956, 580-585.

24 Boulard, Cl., Cabannes, R., Duzer, A., and Scotto, J. A., Hémoglobinose J chez un Algérien musulman atteint d'un retard de développement dystrophique avec splénomégalie, *Sem. Hôpit. Paris, 36,* 1960, 1-7.

prises those that are undoubtedly polymorphic—that is to say, have gene frequencies of the order of 10 percent or thereabouts—and of these there are only four. One is the sickle-cell gene which is widely distributed in Central Africa, the Mediterranean area, and southern Asia. There is thalassemia, which has a very wide distribution through the whole of the Mediterranean area and down to the Far East. There is Hemoglobin C, which has an interesting localization in West

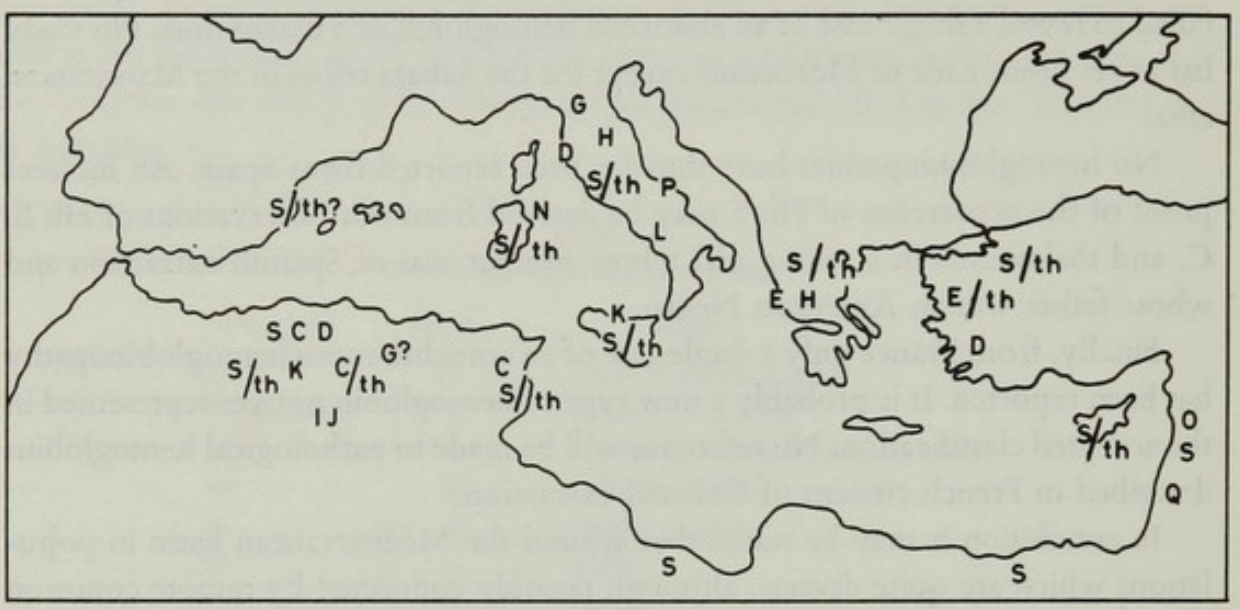


FIG. 12. Distribution of hemoglobinopathies around the Mediterranean Basin.

Africa, although, as pointed out by Dr. Cabannes, it ranges as far north as Algeria. Finally, there is hemoglobin E, which is confined apart from isolated cases to southeast Asia, where there are very high frequencies in Cambodia and vicinity. In other words, we have these four polymorphic genes, and we may expect that the selective agencies affecting these will be quite different from those affecting the second class of hemoglobinopathies. These are due to the rarer abnormal hemoglobins, which have turned up mainly in sporadic cases or in single families and to some of which Dr. Cabannes has alluded.

Now we have considered the hemoglobins, and the next part of this session will be devoted to the detection of the varieties of Glucose-6-Phosphate-Dehydrogenase deficiency and to their distribution. I ask Dr. Motulsky, who has been concerned with developing these techniques, to give us an account of the screening methods and the distribution of these characters.

MOTULSKY: It is generally known that Glucose-6-Phosphate-Dehydrogenase deficiency was first observed in American soldiers returning from Korea who developed hemolytic anemia after administration of primaquine—a new antimalaria drug. Ten percent of American Negro soldiers receiving this drug showed hemolytic anemia, whereas only very few soldiers of Caucasian origin responded to this chemical. A series of investigations, started at the University of Chicago,

under the sponsorship of Dr. Alving and carried out primarily by Beutler, Carson, and their collaborators, resulted in the finding that the enzyme Glucose-6-Phosphate-Dehydrogenase was inactive in the red cells of these individuals (see also p. 75). Further studies by Childs and coworkers in Baltimore showed that this trait was sex-linked. The males of any population in which this trait is common fall clearly, therefore, into two classes, with normal and abnormal enzyme activities.

Initially there was some confusion in the literature about the frequency of this trait, because various tests were also applied to female populations. Since the female heterozygotes in many instances and with many test systems overlap with both the affected and the normal populations, the frequencies of affected males and females appeared similar in some surveys. However, the frequency of affected females (homozygotes plus heterozygotes) should be about twice that of affected males for a fully dominant sex-linked gene so long as the gene frequency is below 15 percent. Meanwhile by application of a direct enzyme assay employing TPNH, most female heterozygotes can be discovered.

Both Beutler's test, based on glutathione stability, and the enzyme assay tests require a spectrophotometer and are therefore unsuitable for field studies. We became interested in this problem and developed a more rapid field screening test[1] which has been used extensively in these surveys.

The enzymatic reaction which is affected in trait carriers is that between Glucose-6-Phosphate and TPN, forming 6-phosphogluconate and TPNH (see also p. 269). We coupled this reaction to a dye, Brilliant Cresyl Blue. This dye, when added to a hemolysate containing Glucose-6-Phosphate and TPN, becomes decolorized within less than one hour if the hemolysate contains normal amounts of the enzyme, whereas in enzyme-deficient hemolysates decolorization requires 2 to 24 hours.[2] This test can be carried out on large numbers of samples under field conditions.

The blood samples can be stored overnight in refrigerated bags, and the test may be delayed until the morning after collecting. As expected, at room temperature the samples deteriorate faster.

The question has been raised whether the decolorization time has to be corrected for variations in hematocrit if the population studied includes anemic subjects. However, such a correction is not necessary except in cases with severe anemia and very low levels of hematocrit. The test has been set up in a manner allowing for a fairly wide variation in hematocrit. All this applies to males, with clear-cut differences between normal and abnormal. When applied to females, however, this system may detect about two-thirds of the heterozygotes if one is very careful in measuring the decolorization time, checking the test system every few minutes, which becomes rather cumbersome.

1 Motulsky, A. G., Population genetics of Glucose-6-Phosphate-Dehydrogenase deficiency of the red cell, in Blumberg, B. S. (Ed.), *Proceedings of a Conference on Genetic Polymorphisms and Geographic Variations in Disease*, Grune & Stratton, New York, 1961.

2 *Ibid.*

Another test system that appears to be very useful is that developed by Alving's group and known as the methemoglobin-reduction test. In this test, hemoglobin is first oxidized to methemoglobin by nitrite. This methemoglobin is dark brown. In a system containing TPN, Glucose-6-Phosphate, and sufficient amounts of G6PD, TPNH will be formed and will reduce the methemoglobin to hemoglobin, the color changing back to red. This system works fairly well on a quantitative basis. We have recently tried to set it up as a screening test for the detection of female heterozygotes and it may well prove useful. Of course, for more intensive study it is best to apply direct enzyme assays.

The distribution of this trait mirrors rather closely that of the abnormal hemoglobins and of thalassemia.[3] The gene is fairly common in some regions of Africa, the highest frequencies having been reported in the Congo. During our survey in the Republic of Congo, we found 20 percent in the metropolitan population of Leopoldville; 24 percent in Bayaka, in southern Congo; 14 percent in the metropolitan population of Stanleyville; 6 percent in a northern Congo population; 4 percent among the Pygmies. For various reasons we think that this low incidence of 4 percent among the Pygmies may be wrong—the concentration may be higher—but owing to the political disturbance in the Congo, we could not resume the test.

G6PD deficiency is certainly a Mediterranean gene; it is found all over the Mediterranean—Sardinia, Sicily, southern Italy, the Po Valley, Greece, Cyprus, Turkey, the Near East, and Israel—and in India and southeast Asia. Last year I did a more detailed study in the Philippines and in Formosa. I had expected a higher frequency from some data we have accumulated on Filipino populations in America, where we found in about 200 specimens an incidence of 12 percent. In another four or five Filipino populations sampled, the incidence was between 4 and 5 percent. The trait has not been found in northern European or North American populations. It has not been found in Alaskan and American Indian populations. It is absent in Japanese populations. In Taiwan the frequency was 3 or 4 percent and it was similar in other Chinese studied. In India the frequency ranges from 3 to 8 percent, both in students in America from India and in various Indian populations. In Iran, especially around the shores of the Caspian Sea, the incidence appears to be high—about 10 percent. The remarkable variation in the concentration of this character exhibited by the Jewish populations will be described by the Israeli investigators.

In summary, this is a very common trait which has reached its highest proportions in certain malarious areas. Whereas the other traits discussed thus far are autosomal, G6PD control depends on a sex-linked polymorphic system, which poses very specific problems in population genetics.

3 *Ibid.*

ALLISON: And now we shall ask Dr. Szeinberg to speak about this character in Israeli populations.

A. SZEINBERG

G6PD Deficiency among Jews—Genetic and Anthropological Considerations*

Glucose-6-Phosphate-Dehydrogenase deficiency is characterized by a restricted geographic and ethnic distribution and by high frequencies of occurrence in some population groups. We are not dealing in this case with rare freaks of nature, as in some other metabolic disorders, but rather with a well-established polymorphism of human populations. This condition is therefore suitable for the investigation of forces which influence the establishment and maintenance of such a polymorphism. In addition, this abnormality may serve in certain circumstances as a marker for retracing the past movements of population groups and for the study of ethnic relationships.

As may be seen from Table I (see also p. 271), this abnormality has been found in virtually all the Jewish communities thus far investigated, but the frequencies of its occurrence vary considerably. The same enzyme deficiency has also been detected in some non-Jewish groups in Israel. I shall limit my remarks to some points that may be of importance for further discussion during this conference.

At the preliminary stages of our survey we thought that the enzyme deficiency was completely absent among the Ashkenazic Jews.[1-3] Subsequently, however, several cases have been detected on random screening of 800 Ashkenazic Jews (0.4 percent frequency). In addition, nine cases of hemolytic anemia due to favism or drugs have been observed by us during the past 3 years in a population of about 1 million Ashkenazic Jews in Israel. These enzyme-deficient subjects came to Israel from Russia, Poland, or Germany.

We think that these findings may be of particular importance from the point of view of geographic population genetics. If future investigations fail to show a similar occurrence of the abnormality among the local populations in European

* The investigations reported in this presentation were supported by grants from the U.S. National Institutes of Health (A 2740) and from the Rockefeller Foundation (RF 60101).

1 Szeinberg, A., Asher, Y., and Sheba, Ch., Studies on glutathione stability in erythrocytes of cases with past history of favism or sulfa-drug-induced hemolysis, *Blood, 13,* 1958, 348-358.

2 Szeinberg, A., Sheba, Ch., and Adam, A. Selective occurrence of glutathione instability in red blood corpuscles of the various Jewish tribes, *Blood, 13,* 1958, 1043-1053.

3 Szeinberg, A., Sheba, Ch., Adam, A., and Ramot, B., A hereditary abnormality of the metabolism of glutathione in red blood cells, *Acta Genet. et Gemell. Suppl. Sec.,* 1959 ,151.

TABLE I

FREQUENCY OF G6PD DEFICIENCY AMONG MALES OF VARIOUS COMMUNITIES (RANDOM SAMPLES)

	Sample size	*% Deficient*
ASHKENAZIM	819	0.4
NON-ASHKENAZIM		
Europe (Sephardim)		
Turkey	256	1.9
Greece and Bulgaria	152	0.7
Others	93	2.2
Asia		
Kurdistan	196	58.2
Iraq	902	24.8
Iran	557	15.1
Caucasus	25	28.0
Afghanistan	29	10.3
Yemen and Aden	415	5.3
Bukhara	46	—
Syria and Lebanon	80	6.3
India (Cochin)	58	10.3
India (Bnei Israel)	102	2.0
North Africa		
Egypt	112	3.8
Morocco	219	0.5
Atlas Mountains	23	1 case
Algiers and Tunisia	112	0.9
Libya	219	0.9
Gerba	52	—
*Ethiopia**		
Fallasha	208	—
OTHER GROUPS		
Samaritans	69	—
Karaites	18	—
Arabs	264	4.4
Druzes	92	4.4
Circassians	57	—

* Investigated in Ethiopia (see footnote 5).

countries from which the Ashkenazim came, these findings will provide a marker demonstrating a common origin of the Ashkenazim and of the other Jewish communities. If, on the other hand, a similar frequency of the gene is found among Poles, Russians, or Germans, the possibility of sporadic mutations in any part of the world will have to be considered; we believe, therefore, that similar large-scale surveys should be performed in the European countries in order to elucidate this basic problem in human population genetics.

The next point which I should like to stress is the extremely high frequency of the abnormality in Kurdistan. The Kurdish Jews seem to be distinguished by the highest frequency of this abnormality thus far recorded for any population (58

percent). However, even this community is not homogeneous. During the initial stages of our survey we were surprised by the finding[4] that almost all the blood samples taken from the village of Maoz Zion, in the Jerusalem mountains, showed an enzyme deficiency. At first a technical error was suspected, but repeated examinations confirmed the results. It was known that all the inhabitants of this village came from a restricted mountainous region of northern Kurdistan (see also p. 275). Subsequently, all Kurdish subjects investigated by us were classified according to their villages or towns of origin, and it was found that the frequency of enzyme deficiency among males from this region was about 70 percent, whereas among those from other parts of Kurdistan it was only about 35 percent (Table I; see also p. 271).

TABLE II

FREQUENCY OF G6PD DEFICIENCY AMONG MALES FROM KURDISTAN, IRAQ AND IRAN

Group designation	*Region*	*Sample size*	*% Deficient*
KURDISH JEWS	*Northern Iraqi Border*		
	(Zakho, Dahok, Sandor, Amadia)	126	70.64
	Iraq-Western Iran		
	(Mosul, Erbil, Kirkuk, Sulemania-Sinandaj, Kermanshah, Qasar-I-Shrin)	59	35.09
IRAQI JEWS	Baghdad	286	24.48
	Mosul, Erbil, Kirkuk	34	52.00
PERSIAN JEWS	*Central Iran*		
	(Teheran, Shiraz, Isfahan)	370	10.80
	Western Iran		
	(Kermanshah, Sinandaj)	45	44.40

Interestingly enough, a similar subdivision became apparent among the Iraqi and Persian Jews. Some of them, coming from southern or eastern Kurdistan, claimed no relationship to the Kurdish community, and yet the frequency of the enzyme deficiency among them was much higher than among the subjects from Baghdad or central Iran (Table II). Thus it appears that the restricted mountainous area in northern Kurdistan constitutes the region of the highest concentration of the enzyme deficiency in the world, with a decreasing gradient toward the south and east. Unfortunately, we have, as yet, no data regarding the non-Jewish population of Kurdistan. Such data would be of great importance, since they could indicate whether this high frequency was caused by genetic drift among the Jews or by some environmental factor operating in this region.

Another interesting finding relates to the people from the Caucasus Mountains (Table I). Although our sample is small, it nevertheless suggests a high frequency of the enzyme deficiency among Jews from that region in contrast to its absence among the Circassians (Moslems from the same area who came to the Turkish

4 Cohen, T., Goldschmidt, E., Adam, A., Matoth, Y., Theodor, E., and Szabo, M. A., The frequency of rheumatic heart disease, glutathione instability, and thalassemia in children of Kurdish Jews, *Harefuah*, *57*, 1959, 233-236.

Empire in the middle of the nineteenth century because of religious persecutions in Russia).

We also find no enzyme-deficient subjects among the Samaritans, who have lived in Palestine since ancient times but whose origins are supposed to be non-Jewish. According to the scriptures (Kings II, 17), the Samaritans were foreign settlers brought over by the Assyrians after the conquest of Samaria (8th century B.C.). At present they constitute a very small community (about 300 persons) which is highly inbred (see also p. 354). Slightly more than half of this community lives in the town of Nablus in Jordan. We have investigated those settled in Israel near Tel-Aviv. These people have lived in a highly malarious region for about 2800 years, and yet we did not find any case of enzyme deficiency among them. The same applies to the Karaites.

No case of enzyme deficiency was detected among the Fallasha, who were studied by our group during an expedition to Ethiopia.[5] Interestingly enough, a similar absence of the enzyme deficiency (and of hemoglobinopathies) was found among 1000 Ethiopians belonging to six different tribes, a fact which places them in a singular position among the African people.

ALLISON: Many people were interested in the reports about the high frequency of this character in Israeli populations. High frequencies have also been found in Sardinians, and Dr. Siniscalco is going to tell us about these.

M. SINISCALCO

Field and Laboratory Studies on Favism and Thalassemia in Sardinia

Before summarizing the data collected by our group on the distribution of G6PD deficiency in Sardinia,[1,2] I should like to point out some difficulties we encountered when we began our investigations. At that time, the relationship between G6PD deficiency and favism had already been indicated by several

5 Adam, A., Bat-Miriam, M., Barnicot, N. A., Lehmann, N., Mourant, A. E., Ramot, B., Sheba, Ch., and Szeinberg, A., A survey of some genetic characters in Ethiopian tribes, Proceedings, Second International Conference on Human Genetics, Rome, 1961. In press.

1 Bernini, L., Carcassi, U., Latte, B., Motulsky, A. G., Romei, L., and Siniscalco, M., Indagini genetiche sulla predisposizione al favismo. III. Distribuzione delle frequenze geniche per il locus Gd in Sardegna. Interazione con la malaria e la talassemia al livello popolazionistico, *R. Accad. Lincei,* Ser. VIII, *29,* fasc. 1-2, 1960, 1-11.

2 Siniscalco, M., Bernini, L., Latte, B., and Motulsky, A. G., Favism and thalassaemia in Sardinia and their relationship to malaria, *Nature, 190,* 1961, 1179-1180.

authors, and the first family data supporting the sex-linkage hypothesis had just been published.[3] There had been, on the other hand, sporadic reports of cases, especially in the Italian literature, which were in open contrast not only with the sex-linkage hypothesis but even with the assumption that favism occurs only in enzyme-deficient subjects. Indeed, our own skepticism was aroused when we met with a few families in which the enzyme deficiency appeared to be transmitted from father to son or in which some females with a positive history of favism showed an enzyme activity within the normal range. We soon realized, however, that these inconsistencies were only apparent and that they were mainly due to misclassification of the red-cell enzyme phenotypes in the presence of thalassemia or in blood samples that had been collected during the peak of the fava-bean season.

It was easy to account for the increase in blood enzyme levels occurring in late spring in most of the heterozygous females and even in some of the totally enzyme-deficient individuals. This is due to the increased proportion of young red cells present in the circulation after prolonged periods of even a mild hemolysis following repeated ingestion of fava beans.

On the other hand, we still lack a satisfactory explanation for the higher enzyme levels in the blood of thalassemic patients. Chromium-51 measurements performed in four groups, each comprising about 20 males, showed a significant reduction of the red-cell life span in the individuals affected with the enzyme deficiency or with the enzyme deficiency plus thalassemia. But strangely enough, the red-cell survival in the enzyme-normal thalassemia carriers turned out to be even longer than in the normal control group. It cannot be decided at this stage whether we are dealing with a genuine increase in red-cell survival or merely with a different rate of chromium elution from thalassemic red cells. (This experiment, which was performed in collaboration with Dr. Adinolfi, Dr. Mollison, and Dr. Piomelli, will be described in detail in a forthcoming publication.)

It may also be worth mentioning that the increase in enzyme activity observed in thalassemic patients is constant throughout the year and that the carriers of both enzyme deficiency and thalassemia appear to be less susceptible to severe episodes of clinical favism.

The population data for 19 Sardinian villages are summarized in Table I, in which the frequencies of G6PD deficiency and of thalassemia are reported for each village together with the altitude and the prevalence of malaria in the past. The positive correlation between the frequencies of the two erythrocyte defects is demonstrated in Figure 13, in which the concentrations of the two genes in 14 Sardinian villages are plotted against each other.

These findings strongly suggest that malaria could have been the ecological

3 Childs, B., Zinkham, W. H., Browne, E. A., Kimbro, E. L., and Torbert, J. V., A genetic study of a defect in glutathione metabolism of the erythrocyte, *Bull. Johns Hopkins Hosp., 102,* 1958, 21.

TABLE I

ENZYME DEFICIENCY AND THALASSEMIA IN SARDINIAN VILLAGES

Village	*Altitude (m.)*	*Malarial frequency* (%)*	*No. examined*	*Enzyme deficiency in males = gene freqnency (± S.E.)*	*Thalassemia gene frequency† (± S.E.)*
Luras	508	78	100	0.070 ± 0.025	0.112 ± 0.022
Usini	190	95	99	0.061 ± 0.024	0.071 ± 0.019
Lodè	345	90	163	0.294 ± 0.035	0.110 ± 0.017
Siniscola	42	55	198	0.113 ± 0.023	0.129 ± 0.024
Benetutti	406	50	100	0.090 ± 0.028	0.060 ± 0.017
Suni	333	85	98	0.143 ± 0.035	0.125 ± 0.023
Orosei	19	93	180	0.140 ± 0.026	0.094 ± 0.012‡
Galtelli	40	96	175	0.120 ± 0.024	0.106 ± 0.014‡
Fonni	1,000	19	100	0.030 ± 0.014	———
Desulo	891	33	313	0.031 ± 0.009	0.018 ± 0.005‡
Tonara	935	10	148	0.040 ± 0.016	0.023 ± 0.010‡
Lanusei	595	25	100	0.040 ± 0.019	———
Tortoli	15	90	50	0.160 ± 0.052	———
Cabras	9	97	200	0.350 ± 0.034	0.140 ± 0.024
S. Giusta	10	97	42	0.309 ± 0.075	———
Terralba	9	97	100	0.300 ± 0.046	———
Isili	523	17	100	0.090 ± 0.029	0.095 ± 0.021
Gergei	374	66	92	0.185 ± 0.040	0.065 ± 0.018
Teulada	50	90	101	0.169 ± 0.037	0.125 ± 0.023

* For reference see Bernini *et al., loc. cit.*

† The gene frequency was calculated as one-half the heterozygote frequency because of lethality of homozygous thalassemia.

‡ From Ceppellini, R., Blood groups and haematological data as a source of ethnic information, in Wolstenholme, G. E. W., and O'Connor, C. M. (eds.), *Medical Biology and Etruscan Origins,* 1959, 177-188.

factor balancing both traits. The selective advantage of the carriers probably derives from the slower multiplication rate of the plasmodium parasites in the metabolically abnormal red cells.

It is generally known that this hypothesis has been confirmed by Dr. Allison in an *in vivo* experiment in which Plasmodium falciparum was injected into two groups of normal and enzyme-deficient nonimmune children. On the other hand, Dr. Sheba (p. 100) has shown that the rates of G6PD deficiency in some Jewish tribes show little correlation with the distribution of malaria.

It must be stressed that this discussion could gain greatly by accurate information on the customs and habits of the populations under study and on their change in historic and prehistoric times. If the malaria hypothesis is valid, the time has come to analyze the efficiency of the selective mechanisms in both settled and nomadic populations. In regard to Sardinia, we may state with confidence that the villages described in Table I represent true and very ancient genetic isolates, whose members show little mobility to the present day.

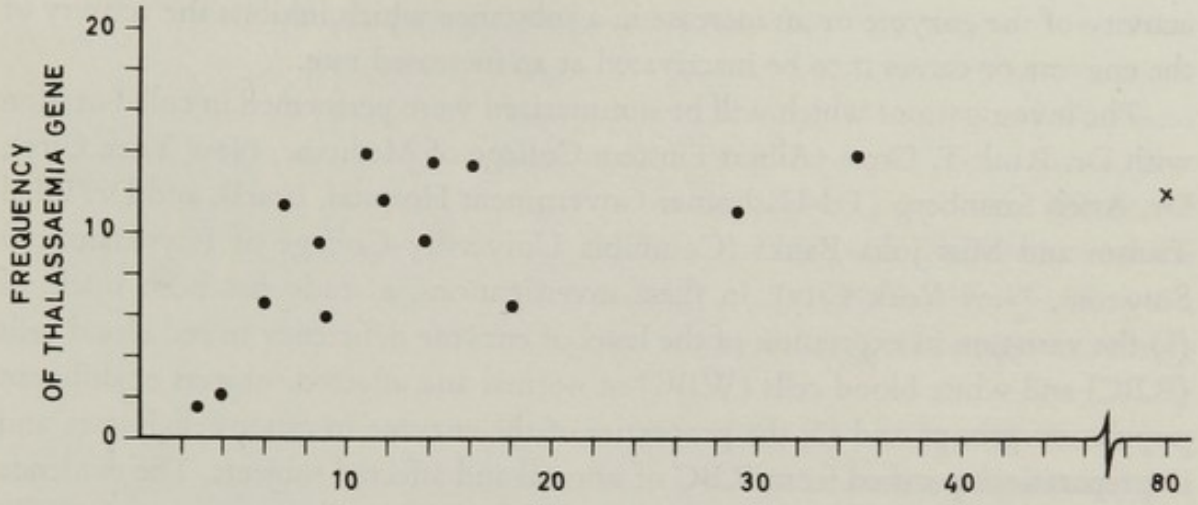


FIG. 13. Gene frequencies of G6PD deficiency and thalassemia in 14 Sardinian villages (•) and in Kurdish Jews in Israel (×).

ALLISON: A further development in this field has come up relatively recently. We already know that thalassemia is a block term including a number of different genetically determined abnormalities, and again this is true of G6PD deficiency. Dr. Marks, who has done some important work in this field, will tell us about this.

P. MARKS

G6PD Deficiency in Different Population Groups*

Our laboratory has been studying the mechanism by which genetic alterations lead to a deficiency in the activity of Glucose-6-Phosphate Dehydrogenase (G6PD) in human subjects. On the basis of investigations, primarily with lower organisms, it may be anticipated that the deficiency in activity of this enzyme could be due to one of several mechanisms. These possibilities include:

(1) that G6PD deficiency results from a mutation which leads to a decrease in the rate of synthesis of the enzyme;

(2) that the low levels of enzyme activity reflect the formation of an altered protein. The enzyme could be altered in its catalytic site so that it has a decreased affinity for the substrate, Glucose-6-P, or the cofactor, TPN. Alternatively, the altered enzyme might be less stable and inactivated more rapidly than the normal enzyme;

* These investigations were supported in part by Grants CY 2332 and RG 7368 of the U.S. Public Health Service.

(3) that the mutation might result in a decrease of a factor essential to the activity of the enzyme or an increase in a substance which inhibits the activity of the enzyme or causes it to be inactivated at an increased rate.

The investigations which will be summarized were performed in collaboration with Dr. Ruth T. Gross (Albert Einstein College of Medicine, New York City), Dr. Arieh Szeinberg (Tel-Hashomer Government Hospital, Israel), and Dr. Ethel Tsutsui and Miss Julia Banks (Columbia University College of Physicians and Surgeons, New York City). In these investigations, a study has been made of (1) the variation in expression of the level of enzyme deficiency in red blood cells (RBC) and white blood cells (WBC) of normal and affected subjects of different population groups and (2) the properties of the enzyme in crude cell lysates and in preparations purified from RBC of normal and affected subjects. The evidence obtained indicates that there are significant differences in the expression of G6PD deficiency and in the properties of the enzyme among certain groups of affected subjects. These data suggest that this enzyme deficiency in man is genetically heterogeneous.

As has been indicated by other speakers, the genetically determined deficiency of G6PD is widespread in occurrence and varies markedly in frequency among different population groups.[1,2] One of the initial indications of a possible genetic heterogeneity among affected subjects was the finding of a significant difference in the severity of the enzyme deficiency in the RBC and in the WBC of affected Negroes compared with affected Caucasians.[3] Thus, among affected Negro males, the level of G6PD in erythrocytes is, on the average, about 15 percent of the mean value for normal subjects, whereas in WBC of these affected subjects, the enzyme activity is either only slightly decreased or within the range of normal. By contrast, affected Caucasians in the New York City population have levels of RBC enzyme reduced, on the average, to 3 percent and levels of WBC enzyme reduced, on the average, to 30 percent of the mean normal activities. The Caucasian population studied represents an ethnically heterogeneous group, but is predominantly of southern Italian extraction. Ramot and co-workers[4] studying this problem among Caucasians of Sephardic Jewish extraction found similar low values of enzyme activity in RBC and WBC of affected subjects. No differences have been detected between affected Negro and Caucasian females with respect to RBC and WBC enzyme levels.

1 Beutler, E., Drug-induced hemolytic anemia, in Stanbury, Syngaarden, and Frederickson (eds.), *The Metabolic Basis of Inherited Disease*, McGraw Hill, New York, 1960, p. 1031.

2 Marks, P. A., Biochemical aspects of red cell aging and drug induced hemolytic anemia: A review, Nouvelle Revue d'Hématologie, 1961. In press.

3 Marks, P. A., and Gross, R. T., Erythrocyte glucose-6-phosphate-dehydrogenase deficiency. Evidence of differences between Negroes and Caucasians with respect to this genetically determined trait, *J. Clin. Invest., 38,* 1959, 2253-2262.

4 Ramot, B., Fisher, S., Szeinberg, A., Adam, A., Sheba, C., and Gafni, D., A study of subjects with glucose-6-phosphate-dehydrogenase deficiency. II. Investigation of leucocyte enzyme, *J. Clin. Invest., 38,* 1959, 2234-2237.

Affected females of both groups have, on the average, about a 50-percent decrease in RBC enzyme activity and normal leukocyte G6PD levels. As has been indicated by previous speakers, affected females are predominantly heterozygous (this trait appears to be due to a sex-linked gene in both Negro and Caucasian populations), and this may be reflected in the findings that the level of the enzyme in the vast majority of affected females is intermediate between that of affected males and normal subjects. The finding of similar values for the activity of the enzyme in affected Negro and Caucasian females may mean that the presence of a single normal gene could mask quantitative differences in the enzyme activity which might result from different mutant genes.

Recently, a family was encountered in northern Italy (Barbieri family) in which affected males have only about a 50-percent decrease in erythrocyte G6PD activity and normal levels of the WBC enzyme. The activity of G6PD in RBC and WBC of affected males in this family is indistinguishable from that of affected females of this family or of other population groups.[5] Dr. Gross will discuss our studies of this family in more detail (see p. 83).

Further evidence suggesting that the G6PD defect may not reflect the same genetic alteration in all affected persons was obtained from studies of the stability of the enzyme in crude cell lysates. Studies in several laboratories indicated that G6PD of affected subjects compared to that of normal persons was less stable in crude hemolysates incubated at 38°C.[6-8] Experiments were performed comparing the stability of G6PD in hemolysates and leukocyte lysates prepared from cells of normal subjects and affected Negroes and Caucasians (Fig. 14). In these studies, the enzyme of affected Caucasians was less stable than that of affected Negroes or of normal subjects. The enzyme in hemolysates prepared from affected Negroes was less stable than that of normal subjects, but no striking difference between these two groups was observed with respect to the stability of the enzyme in leukocyte lysates.

The marked decrease in stability of G6PD in both RBC and WBC of affected Caucasians and the moderate decrease in RBC of affected Negroes could be a consequence of the initial lower concentrations of active enzyme in affected cell lysates, the lower concentration of enzyme being associated with a decreased stability of the protein. The evidence that we have obtained does not support this possibility. The differences in stability of G6PD are apparent even when hemolysates prepared from normal subjects or from affected Negroes are diluted with

5 Marks, P. A., Szeinberg, A., and Banks, J., Erythrocyte glucose-6-phosphate dehydrogenase of normal and mutant human subjects, *J. Biol. Chem., 236,* 1961, 10-17.

6 Carson, P. E., Schrier, S. K., and Alving, A. S., Inactivation of glucose-6-phosphate dehydrogenase in human erythrocytes, *J. Lab. Clin. Med., 48,* 1956, 794-795.

7 Szeinberg, A., Sheba, C., and Adam, A., Enzymatic abnormality in erythrocytes of a population sensitive to Vicia faba or haemolytic anaemia induced by drugs, *Nature, 181,* 1958, 1256.

8 Marks, P. A., Banks, J., and Gross, R. T., Glucose-6-phosphate-dehydrogenase thermostability in leucocytes of Negroes and Caucasians with erythrocyte deficiency of this enzyme, *Biochem. Biophys. Res. Comm., 1,* 1959, 199-202.

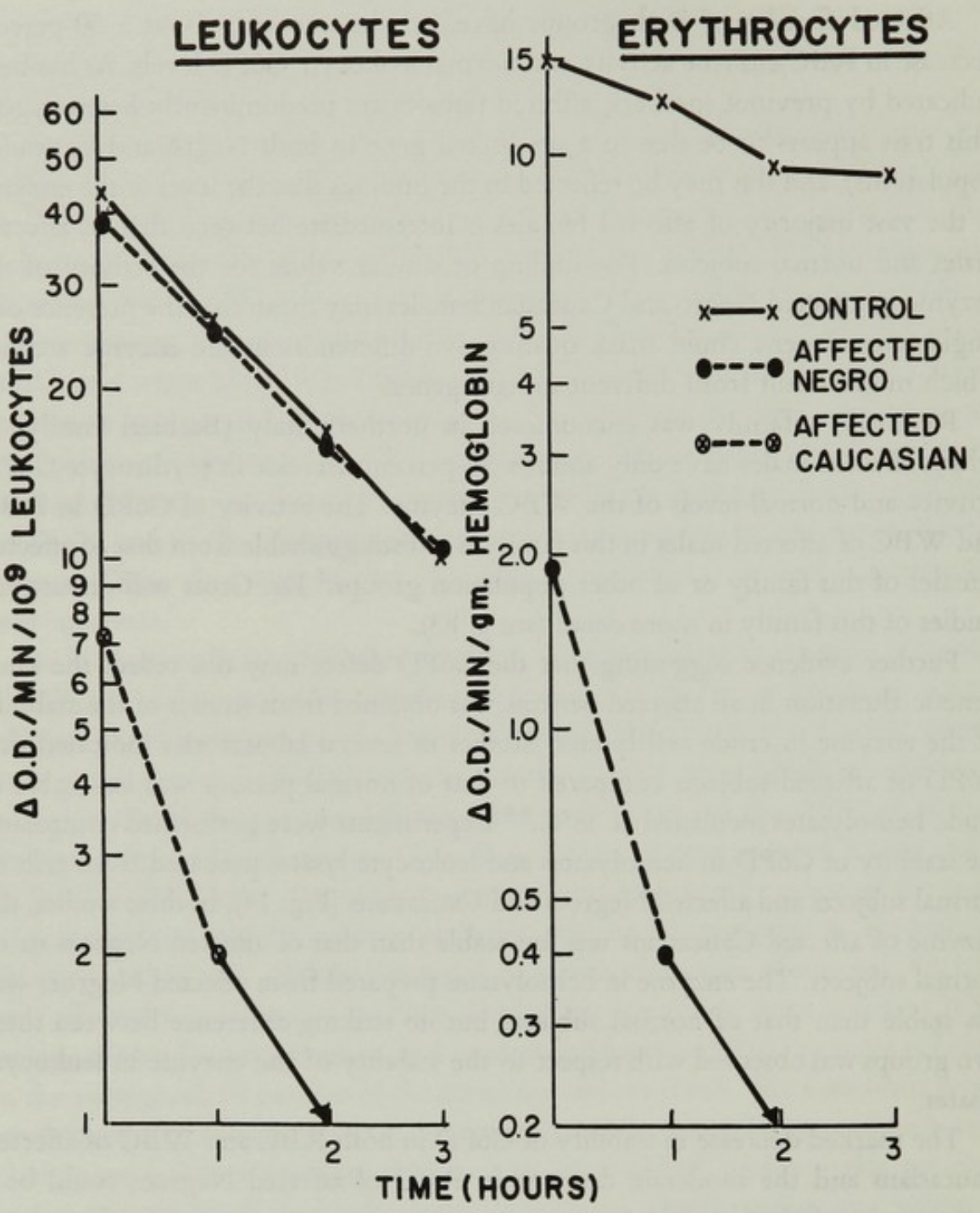


FIG. 14. Stability of G6PD activity in lysates of erythrocytes and of leukocytes incubated at 38°C. (see footnote 8). The solid lines projected with the arrow indicate that the enzyme activity decreased to a value below 1 O.D./Min/10⁹ Leukocytes.

buffer solution to a concentration of active enzyme comparable to that in hemolysates prepared from RBC of affected Caucasians. In addition, when mixtures of hemolysates prepared from affected and from normal subjects were incubated, the curve of inactivation of G6PD was as would be predicted on the basis of a summation of the components of the mixture without evidence of an effect of a constituent of one hemolysate on the enzyme activity in the other hemolysate.

Further evidence that G6PD deficiency may be genetically heterogeneous has been obtained from studies of the properties of the enzyme purified from erythro-

TABLE I

PROPERTIES OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE PURIFIED FROM RED CELLS OF NORMAL SUBJECTS AND PERSONS WITH A DEFICIENCY IN THIS ENZYME*

Subjects†	RBC Enzyme Activity‡ Units/gm Hb	K_m TPN $M \times 10^{-6}$	K_m G6P $M \times 10^{-5}$	K_m 2-D-G6P $M \times 10^{-3}$	K_m Nicotinamide $M \times 10^{-2}$	*p*H Optimum§	Electrophoresis‖ %
	NORMAL (7)						
	11.5—18.2	3.4—7.1	3.5—5.6	3.0—3.6	2.0	8.5—9.3	100.0
	AFFECTED						
Negro Males (4)	1.2—4.1	4.4—8.0	3.7—4.1	4.2—5.0	2.0—3.0	8.5—9.3	100.0
Negro Female	8.7	3.6	4.0	4.0	2.0	8.5—9.3	100.0
Barbieri Males (2)	6.5—7.2	12.0—28.0	5.6—8.0	2.5—5.9	2.0	8.5—9.3	135.0
Barbieri Female	8.0	24.0	6.6	5.0	2.0	8.5—9.3	131.0
Caucasian (VP) Male	0.9	9.2	4.6	4.5	—	8.5—9.3	100.0
Caucasian/Negro (GG) Male	0.5	15.0	8.0	—	—	8.5—9.3	100.0
Caucasian (DH) Female	0.8	5.0	2.8	—	—	8.5—9.3	100.0
CNHA¶	0.2	6.0	7.5	—	—	9.0—9.6	—

* For details of methods employed to purify the enzyme and obtain the data included in this table see footnote 5. All determinations were performed in duplicate. Where more than one value is indicated, the figures are the range of values obtained on the multiple samples.

† The enzyme was purified from red cells of the various subjects. The number in parentheses indicates the number of subjects studied in each group.

‡ A unit of activity is defined as an amount of enzyme required to cause a change in optical density of .001 units per minute.

§ These figures represent the range of the *p*H optimum.

‖ The migration of the enzyme is expressed relative to the migration of the normal enzyme. Migration is toward the + electrode, and values greater than 100 percent represent increased mobility of the enzyme relative to the normal enzyme.

¶ This subject, a Caucasian male of southern Italian extraction, had congenital non-spherocytic hemolytic anemia.

cytes of normal subjects and of affected subjects without anemia. The enzyme has been purified 5000-fold from RBC of normal subjects, and from RBC of affected subjects about 500-fold.[9-11] Employing preparations of the enzyme of comparable specific activity (units of enzyme activity per mg. of protein) as well as preparations of the enzyme purified to a comparable degree based on the initial specific activities, studies have been made of the properties of the catalytic sites, electrophoretic mobility, heat stability, and the characteristics of the antigenic sites. A portion of these data is summarized in Table I. The immunochemical studies will be presented below. The enzyme purified from RBC of affected Negro males or of affected Negro females does not differ from the normal with respect to the various parameters included in Table I.

This is in agreement with previous studies employing cruder preparations of

9 Marks, P. A., *loc. cit.*

10 Marks, P. A., Szeinberg, A., and Banks, J., *loc. cit.*

11 Marks, P. A., Gross, R. T., and Banks, J., Genetic heterogeneity of glucose-6-P dehydrogenase deficiency: A variant in mode of expression and properties of purified enzyme. *Nature*, 1961. In press.

the enzyme.[12, 13] The properties of the enzyme of an affected Caucasian female (Subject DH, Table I) were also found to be similar to those of the enzyme of normal subjects. On the other hand, the enzyme purified from each of three affected members of the Barbieri family had an altered affinity for TPN and an altered electrophoretic mobility characterized by an increased rate of migration toward the anode.[14] Two affected subjects, a male of mixed Negro-Caucasian parentage (Subject GG, Table I) and a male of southern Italian extraction (Subject VP, Table I), have been found to have enzymes altered in affinity for TPN but differing in no other way from the normal enzyme with respect to the characteristics studied.

Kirkman[15] has reported that G6PD purified from a patient with non-spherocytic hemolytic anemia and G6PD deficiency was altered in its affinity for Glucose-6-P and TPN and in its *p*H optimum. Studies in our laboratory of the enzyme purified from a subject with a similar clinical syndrome revealed no alteration in affinity for TPN but a possible decrease in affinity for G6P and a shift in the *p*H optimum. However, these changes are small and their significance is difficult to evaluate.

To further elucidate possible differences in the properties of the enzyme purified from RBC of affected and normal subjects, immunochemical studies have been done. For these studies, an antiserum to C6PD purified from RBC of normal subjects was prepared in rabbits. To date, this serum has been tested against the enzyme of four normal subjects, two affected Negro males, an affected Negro female with intermediate activity, an affected Caucasian male (Subject VP, Table I) and an affected Caucasian female (Subject DH, Table I). In each instance, the antiserum was found to react with the enzyme of affected subjects. The antiserum forms a precipitate with the preparation of the enzyme and inhibits its activity.

The curve obtained upon addition of increasing amounts of enzyme to a constant amount of antiserum is illustrated in Figure 15 for preparations of the enzyme purified from RBC of a normal subject and an affected Negro male. The curves of inhibition of the enzyme by the antiserum appear to be similar in the zone where the antigen is present in large amount for each of the normal and affected enzyme preparations studied. However, with two of the five enzyme preparations of affected subjects tested there may be a difference in these curves in the zone of antibody excess. Whether this difference is significant requires examination of additional normal enzyme preparations to permit an accurate determination of the variation in enzyme inhibition in the zone of antibody excess. Use of the Ouchterlony agar gel diffusion technique for analysis of the possible identity of

12 Marks, P. A., Szeinberg, A., and Banks, J., *loc. cit.*

13 Kirkman, H. N., Characteristics of glucose-6-phosphate dehydrogenase from normal and primaquine sensitive erythrocytes, *Nature, 184,* 1959, 1291-1292.

14 Marks, P. A., Gross, R. T., and Banks, J., *loc. cit.*

15 Kirkman, H. N., Riley, H. D., Jr., and Crowell, B. B., Different enzymic expression of mutants of human glucose-6-phosphate dehydrogenase, *Proc. Nat. Acad. Sc., 46,* 1960, 938.

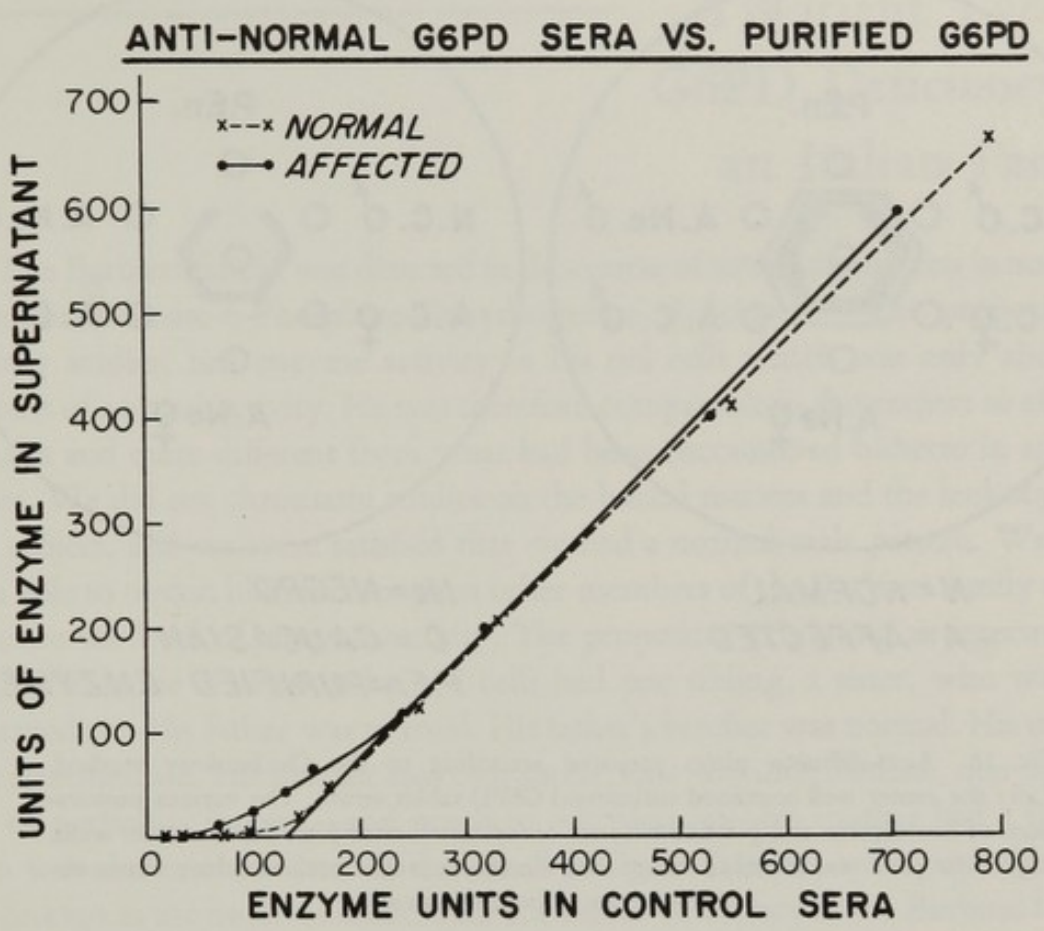


FIG. 15. Curve of inhibition by antinormal G6PD rabbit serum of the activity of G6PD purified from RBC of a normal subject and an affected Negro male. The incubation mixtures contained a constant amount of rabbit antiserum and varying amounts of the preparations of enzyme. The control mixtures were identical except that they contained rabbit serum obtained prior to immunization of the rabbit. The mixtures, after incubation at 37°C. for 30 minutes and then at 4°C. for 18 hours, were centrifuged, and the enzyme activity in the supernatant fluid was determined.

the enzyme preparations from normal and affected subjects indicated no apparent differences among the several affected and normal subjects studied (Fig. 16). This technique may not be as discriminating as the enzyme-inhibition studies for detecting differences in immunochemical properties of the various enzyme preparations.

In none of the affected subjects has there been evidence of a lack of a stromal activator such as that reported by Ramot and co-workers[16] or of an increase in stromal inactivator of G6PD.[17] This suggests the possibility that the striking decrease in the stability of G6PD in crude cell lysates observed for certain affected

16 Ramot, B., Ashkenazi, I., Rimon, A., Adam, A., and Sheba, C., Activation of glucose-6-phosphate dehydrogenase of enzyme-deficient subjects. II. Properties of the activator and the activation reaction, *J. Clin. Invest., 40,* 1961, 611-616.

17 Marks, P. A., and Szeinberg, A., Stabilization and inactivation of glucose-6-phosphate dehydrogenase of normal and mutant subjects, *Fed. Proc., 19,* 1960, 193.

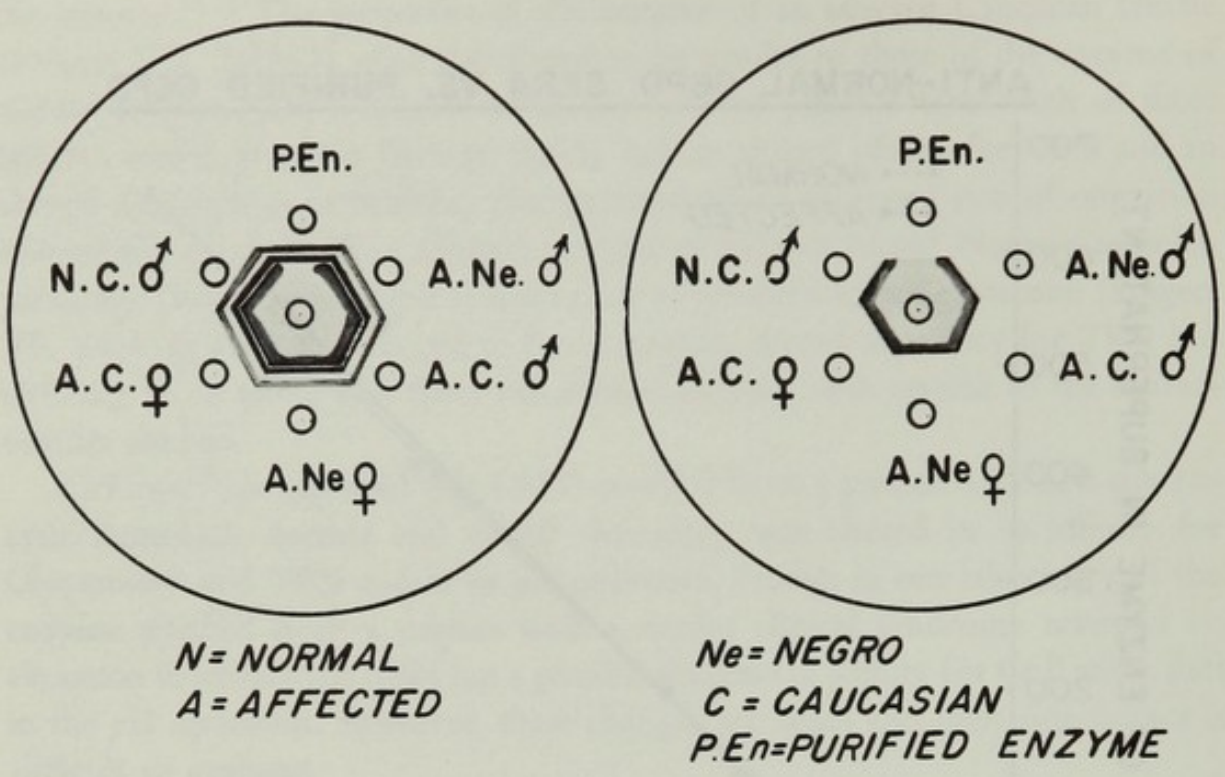


FIG. 16. Agar-diffusion plates prepared according to the Ouchterlony method. *Left*: the center well contained antinormal G6PD rabbit serum. The various preparations of hemolysates and purified enzyme, as indicated, were placed in the outer wells. *Right*: the plate was identical except that the center well contained rabbit serum obtained prior to immunization.

subjects may reflect the formation of an altered enzyme which is more susceptible to an inactivator present in normal amounts.[18, 19]

In summary, studies have been reviewed which have compared the properties of the G6PD in normal subjects and in persons of different population groups with a deficiency of this enzyme. Differences have been found in the expression of this defect among groups of affected subjects. Alterations in the properties of the enzyme in crude and purified preparations have been detected in certain affected subjects. These differences in the characteristics of G6PD deficiency among various affected persons could reflect the fact that this enzyme deficiency in man is genetically heterogeneous. Further studies of the properties of the normal enzyme are required to define the precise nature of the molecular difference between the G6PD of normal persons and that of various affected subjects.

ALLISON: I shall now ask Dr. Ruth Gross to give a few more details about this very interesting family from northern Italy.

18 Marks, P. A., *loc. cit.*
19 Marks, P. A., and Szeinberg, A., *loc. cit.*

R. GROSS

A Variant Type of G6PD Deficiency in an Italian Family

The Barbieri family was detected in the course of screening subjects in northern Italy for Glucose-6-Phosphate-Dehydrogenase deficiency.* The propositus, a healthy soldier, had enzyme activity in his red cells which was only about 50 percent of normal activity. He was therefore comparable in this respect to affected females and quite different from what had been encountered hitherto in affected males. We did sex chromatin studies on the buccal mucosa and the leukocytes of this subject, and we were satisfied that we had a normal male pattern. We were then able to obtain blood from seven other members of the Barbieri family and to examine the level of enzyme activity. The propositus exhibiting an intermediate level of enzyme activity in his red cells had one sibling, a sister, who was also intermediate. His father was normal. His father's brother was normal. His mother was intermediate. His mother had two sisters; one was intermediate, one normal, and of particular interest—and much to our pleasure—his mother had a brother who was also intermediate. In this small pedigree the data are compatible with sex-linkage as the mode of inheritance for G6PD deficiency in the Barbieri family, but, of course, they are insufficient to establish a definitive conclusion on this point.

It should be added that we were able to do hemoglobin determinations, red-cell counts, and reticulocyte counts on all of these subjects, and we found all to be normal. None of the subjects had a history of anemia.

Dr. Marks has already referred to the unique characteristic of this family—namely, the enzyme level of the male propositus and his uncle, which is approximately 50 percent of the normal value, comparable to that which is encountered in affected females in other families and in affected females in this family and certainly different from that which has been observed in affected males in either Negro or Caucasian groups. The white-cell enzyme levels measured in three of the members of this family—the propositus, his affected uncle, and his sister—were found to be normal. We also measured the thermal stability of the enzyme in the crude hemolysate, and this was normal. The enzyme was not activated by the addition of stroma from normal red cells.

The purified enzymes of the propositus, his uncle, and his sister were studied and the Michaelis constants for TPN and for Glucose-6-Phosphate were determined. The point I should like to make is that the Michaelis constant for TPN was significantly increased in all three of the members of this family. There seemed to

* These investigations were performed in part at the Istituto di Genetica, Pavia, Italy, with the cooperation of Dr. L. L. Cavalli-Sforza. The studies of the purified enzyme were performed in the laboratory of Dr. Paul A. Marks of Columbia University in New York in collaboration with Dr. Marks and Miss Julia Banks.

be a normal K_m for Glucose-6-Phosphate, and we found no difference from normal in the *p*H optimum (see also Table I, p. 79). We then studied the electrophoretic mobility on starch gel of the enzyme purified 500-fold. The location of G6PD was identified by specifically staining for the enzyme.

As can be seen in Figure 17, the two members of the Barbieri family—Nos. 3 and 7—showed an electrophoretic mobility which was faster than that of two

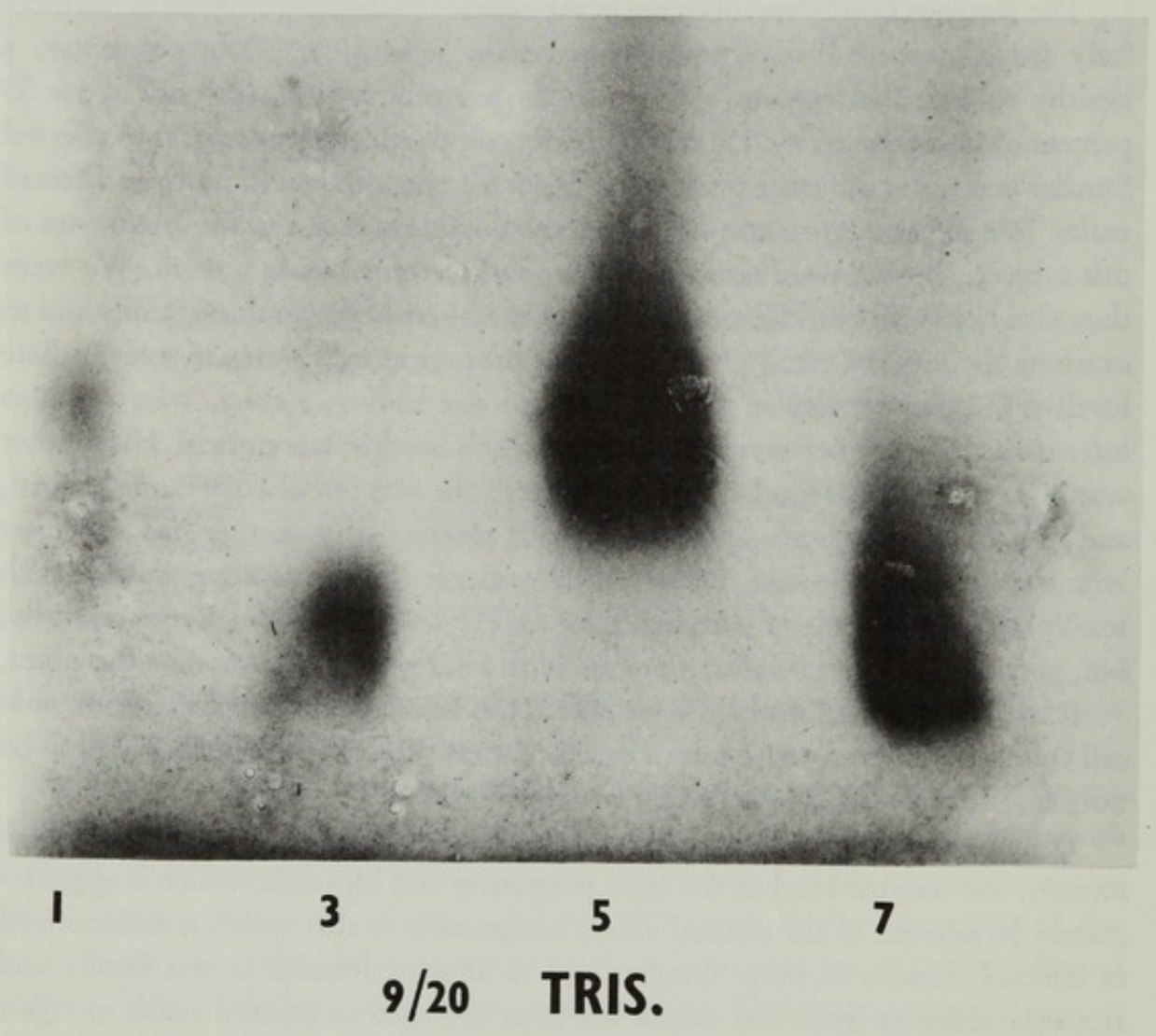


FIG. 17.

normal controls, Nos. 1 and 5. The difference in the size of the spots reflects only the amount of enzyme that was applied. This difference in electrophoretic mobility was found in the three members of the family whom we were able to study, and it is the only such difference that we have encountered. Other affected Caucasians and Negroes have not shown this difference in electrophoretic mobility of the purified enzyme.

In summary, then, we feel that we have encountered in this family a variant of G6PD deficiency. This variant is characterized by a difference in enzyme activity in the affected males which is comparable to that ordinarily encountered in females and quite different from the level usually seen in males. It is also characterized by a

difference in the catalytic site of the purified enzyme and by a difference in the electrophoretic mobility of the enzyme. The data would seem to indicate that the mutant gene is another allele at the locus determining G6PD synthesis. But other possibilities, such as the existence of an entirely different nonallelic gene, which might even be autosomal, cannot be ruled out.

ALLISON: And now Dr. Ramot is going to give a brief account of some work she has done recently.

B. RAMOT

Remarks on the Heterogeneity of G6PD Deficiency

In view of the worldwide distribution of this enzymatic defect, we felt that one of the approaches to the heterogeneity of G6PD deficiency was the study of the enzyme activity in various tissues. For this purpose we studied the G6PD activity in platelets, leukocytes, liver, skin, and saliva of normal and "mutant" subjects. We found in our mutants low G6PD activity in all those tissues. However, in the red cells the enzyme activity was much lower than in all other tissues examined (see Fig. 18). For example, in the leukocytes and platelets, there was about 15 to 20 percent of enzyme activity as compared with normal, whereas in red cells about 4 percent of the normal activity was observed. At the same time, Dr. Marks and Dr. Gross[1] have been studying affected populations of Negroes and Caucasians in New York. As Dr. Marks has mentioned, they found a virtually normal enzyme level in the leukocytes of mutant Negroes and very low enzyme levels in mutant Caucasians. These data can be interpreted in two ways: (1) the affected Jewish populations may have a different mutation from that of affected Negroes; or (2) the higher enzyme activity in the cells of affected Negroes may be due to a difference in the expression of the same mutation.

These different populations also varied on another criterion—namely, the G6PD activity in young red cells vs. the whole red-cell population. The method used was the differential hemolysis described by Marks and collaborators.[2] On this criterion, heterogeneity was found among the mutant Jews themselves (see Fig. 19). In most of the subjects studied, the enzyme level in young cells was significantly higher than in the whole red-cell population. However, in some of the blood samples the young cells as well as the old ones had virtually no enzyme activity.

1 Marks, P. A., and Gross, R. T., Erythrocyte Glucose-6-Phosphate-Dehydrogenase deficiency. Evidence of differences between Negroes and Caucasians with respect to this genetically determined trait, *J. Clin. Invest., 38,* 1959, 2253-2262.

2 Marks, P. A., Johnson, A. B., and Hirschberg, E., Effects of age and the enzyme activity in erythrocytes, *Proc. Nat. Ac. Sc.* (N.Y.), *44,* 1958, 529-536.

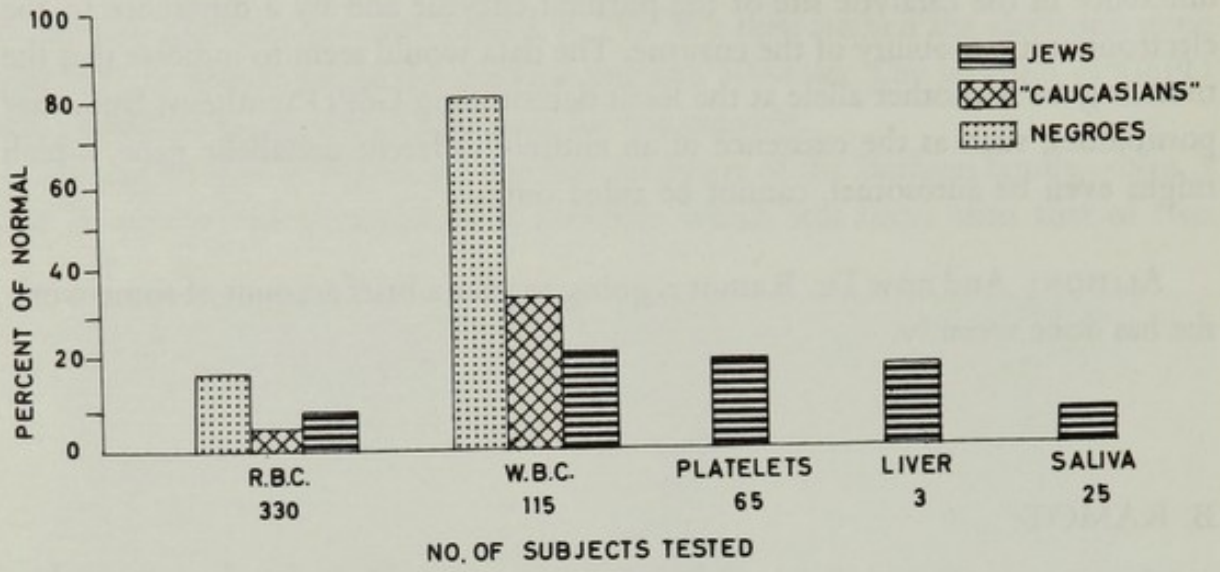


FIG. 18. G6PD activity in tissues of enzyme-deficient subjects of different origin. The data on "Caucasians" and Negroes are based on results of Marks and Gross (see footnote 1). The data on Jews are based on work of the Tel-Hashomer group.

On the other hand, Marks and collaborators[3] found very low enzyme levels in young red cells of mutant Caucasians. Since the sample examined was small, many more subjects should be investigated before a final conclusion is drawn on this point.

Finally, Kirkman[4] has demonstrated the presence of an abnormal G6PD in a case of congenital nonspherocytic hemolytic anemia, and Dr. Gross has described an additional mutation in the Barbieri family. All the data mentioned strongly suggest heterogeneity of this enzymatic defect.

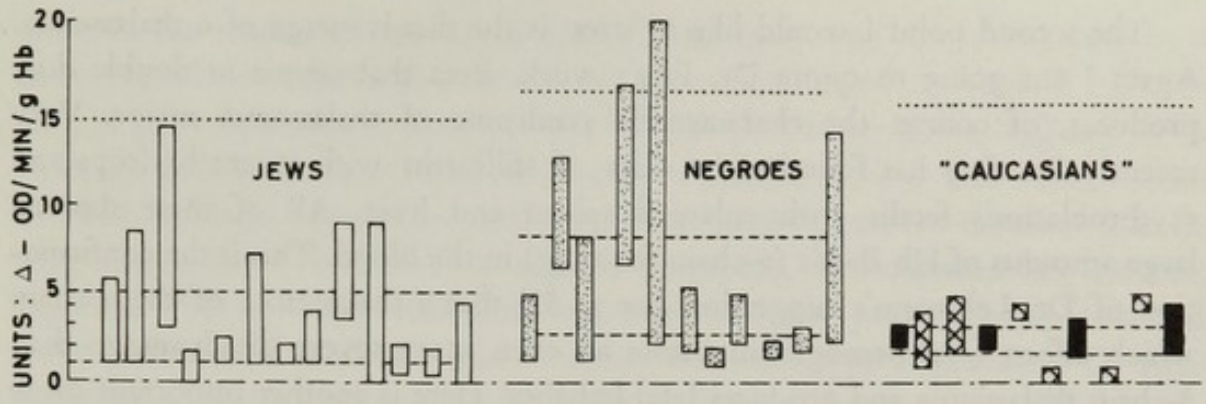
Lately we have begun a new immunological approach to this problem by preparing an antiserum against G6PD. We find that our antiserum inhibits the leukocyte and the platelet G6PD of mutant subjects to a similar degree as the enzyme of the same cell types obtained from normal subjects. We have no data on red-cell G6PD of mutants since we were unable to get a purified concentrated G6PD preparation from their erythrocytes.

I want to emphasize that the antiserum we have prepared is quite different from the one Dr. Marks has obtained, since we get our maximal inhibition, which is 90 to 100 percent, at 15 min. (using either a 500-fold purified enzyme or a hemolysate), whereas the antiserum Dr. Marks mentioned produces the inhibition much more slowly and never approaches the level of inhibition observed by us. Using this method, we were able to prove heterogeneity of erythrocyte G6PD among different animals and we have strongly suggestive evidence of heterogeneity of G6PD in different tissues.

ALLISON: Thank you very much. And now we will go on to the second part of this morning's theme, which concerns the selection operating on the characters

3 *Ibid.*

4 Kirkman, H. N., Characteristics of Glucose-6-Phosphate Dehydrogenase from normal and primaquine sensitive erythrocytes, *Nature*, *184*, 1959, 1291-1292.



..... Mean of whole RBC population of normal subjects.
- - - - - - - - - - Mean of young RBC population of deficient subjects.
—·—·—·— Mean of whole RBC population of deficient subjects.

FIG. 19. G6PD level of whole RBC populations of enzyme-deficient subjects. Each bar represents the difference between young RBC and whole RBC of a single individual. Top of each bar: G6PD in young RBC. Bottom of each bar: G6PD in whole RBC. The data on Negroes and "Caucasians" are based on Marks *et al.* (see footnote 2).

we have been dealing with. I think we can cover very quickly the selection operating against the thalassemia and sickle-cell genes, because it is well known that the homozygous conditions of both these characters produce very severe disease. Indeed, in Africa there is good evidence that the homozygous sickle-cell condition has a fitness which is very nearly zero, and it is also true that the homozygous condition of thalassemia produces a most severe disability which reduces fitness to very low levels. Moreover, evidence is accumulating that the sickle-cell heterozygotes can be at a disadvantage, and Dr. Motulsky is going to review briefly some of the recent work on this point.

MOTULSKY: I would like to refer to two points, to one of which Dr. Neel may be leading. One of these is a recent paper by McCormick,[1] a pathologist in Memphis, discussing the pathology of the sickle-cell trait. In his material of 1100 autopsy cases he had 120 sickle-cell trait cases. It is remarkable that in five cases, four of which were below 2 years of age, the sickle-cell trait had been the cause of death from thrombosis during acute infectious disease. In another 15 cases, he felt—maybe less clearly—that the sickle-cell trait was a major contributing factor to death. Most of these cases were between 40 and 50 years of age, and two were less than 1 year of age.

These findings demonstrate that the sickle-cell trait may be definitely disadvantageous and even lethal in a Western environment. If this is true in the southern United States, the sickle-cell trait in Africa may be even more disadvantageous. In order to explain the genetic balance of the sickling trait, therefore, we must take account of selection not only against the homozygotes but also against the heterozygotes. The age distribution of the trait carriers should be studied in the United States as well as in Africa.

1 McCormick, W. F., Abnormal hemoglobins II. The pathology of sickle-cell trait, *Am. J. Med. Sc.*, *241*, 1961, 329-335.

The second point I would like to stress is the disadvantage of α thalassemia. Again I am going to quote Dr. Eng's work. Beta thalassemia in double dose produces, of course, the characteristic syndrome of thalassemia major. Very recently Dr. Eng has found eight cases of stillbirths with severe hydrops and erythroblastosis fetalis with enlarged spleen and liver. All of these showed large amounts of Hb Bart's (γ-chain tetramer) in the blood. This is the confirmation of Dr. Lehmann's suggestion (see p. 52) that a thalassemia of the α chain which affects fetal hemoglobin causes an even more severe disadvantage than β-chain thalassemia and produces fetal lethality. Here is another important cause of hemolytic disease of the newborn in those areas of the world, such as southeast Asia and India, where α thalassemia occurs.

ALLISON: Now we are going to discuss the selection which operates against G6PD deficiency. One of the interesting things that has come up in the past year or two is the evidence that this condition produces hemolytic disease in the newborn. A number of cases have been found in Greece, and Dr. Fessas will report on these.

PH. FESSAS

Familial Neonatal Jaundice Associated with G6PD Deficiency

It may be appropriate to mention at this point that several years ago, before anything was known about G6PD abnormalities, attention was drawn by Morganti and Beolchini[1] to a particular type of neonatal familial hemolytic disease occurring in the Italian newborn in the absence of incompatibility. Apparently, at that time, the evidence of these workers was received with some skepticism. Meanwhile several reports have appeared which indicate clearly that in certain populations severe neonatal jaundice becomes manifest in G6PD-deficient individuals.[2-6] The circumstances in which the jaundice develops are far from

1 Morganti, G., and Beolchini, P. E., Considerazioni sulla esistenza e frequenza di casi di ittero familiare del neonato senza segni sierologici di immunizzazione maternofetale, Proceedings, 1 Congresso Giuliano di Nipiologia, Trieste, 1950.

2 Panizon, F., Severe icterus of the newborn associated with a deficiency in Glucose-6-Phosphate Dehydrogenase, *Biol. Neon., 2,* 1960, 167-177.

3 Smith, G. D., and Vella, F., Erythrocyte enzyme deficiency in unexplained kernicterus, *Lancet, i,* 1960, 1133-1134.

4 Doxiades, S. A., Fessas, Ph., and Valaes, T., Erythrocyte enzyme deficiency in unexplained kernicterus, *Lancet, ii,* 1960, 44-45.

5 Weatherall, D. J., Enzyme deficiency in haemolytic disease of the newborn, *Lancet, ii,* 1960, 835-837.

6 Doxiades, S. A., Fessas, Ph., Valaes, T., and Mastrokalos, N., Glucose-6-phosphate-dehydrogenase deficiency; a new aetiological factor of severe neonatal jaundice, *Lancet, i,* 1961, 297-301.

clear. In the studies of the Greek group[7,8] an exogenous factor was present in about one-third of the cases—mostly the administration of a vitamin K analogue and, in a few instances, exposure to naphthalene. However, in the majority of the cases it could not be demonstrated, in spite of a careful search, that either mother or child had been exposed to such agents. No such factors are mentioned in the case reports from Sardinia;[9] as regards Singapore, this question has not been clarified.[10] We are thus confronted with two important problems: (1) How high is the incidence of morbidity and mortality from this type of jaundice? (2) After exclusion of exogenous causes, what is the mechanism that triggers off this type of neonatal jaundice?

At present, our answers are of necessity incomplete; however, it is hoped that other investigators will collect data to supplement our knowledge. It may be appropriate to quote a few more recent figures from our studies: G6PD deficiency occurs in 2.75 percent of our random population of newborn males delivered at the Alexandra Maternity Hospital in Athens. Figures on the prevalence of this abnormality in certain parts of Greece have recently been published by Zannos-Mariolea and Kattamis.[11] G6PD deficiency has been found in about two-thirds to three-fourths of our cases affected with severe icterus of unknown etiology developing in full-term infants.[12] The frequency of this type of jaundice is difficult to assess. In Greece it may be as common as hemolytic disease of the newborn due to Rh-immunization. After exclusion of all cases in which exposure to some drug or chemical could be demonstrated and of all cases referred to the hospital after development of jaundice, we have established an incidence of the severe form of this type of jaundice in approximately 1 newborn per 1000 births (over a period of 3½ years, precisely 30 cases of icterus on the basis of G6PD deficiency among 30,000 births). Among males only, there were 23 affected infants among about 15,000 full-term males, an incidence of 1.53 percent per thousand. For female births, there were 0.47 per thousand. The affected male : female ratio is lower than in childhood favism (9 : 1). On the basis of these figures, it can be estimated that approximately 5 percent of the population of newborn males with enzyme deficiency develop severe jaundice. In a more direct approach to this problem, among 800 unselected cord bloods of male infants screened for G6PD deficiency, 22 with enzyme deficiency were found; none of these infants developed severe jaundice, but a larger series may still be desirable.

Another line of investigation which may reveal data of interest is provided by

7 Doxiades, S. A., Fessas, Ph., and Valaes, T., *loc. cit.*
8 Doxiades, S. A., Fessas, Ph., Valaes, T., and Mastrokalos, N., *loc. cit.*
9 Panizon, F., *loc. cit.*
10 Smith, G. D., and Vella, F., *loc. cit.*
11 Zannos-Mariolea, L., and Kattamis, Ch., Glucose-6-phosphate-dehydrogenase deficiency in Greece, *Blood, 18,* 1961, 34–47.
12 Doxiades, S. A., Fessas, Ph., Valaes, T., and Mastrokalos, N., *loc. cit.*

the familial occurrence of this type of jaundice. Thus, among 32 male siblings of G6PD-deficient newborn affected by severe neonatal jaundice, there were 14 cases of severe icterus and only 3 cases of enzyme-deficient brothers who had not been affected. This high incidence of severe jaundice in the enzyme-deficient siblings of the propositi may be contrasted with the absence of jaundice in the enzyme-deficient males ascertained through a random sampling. Although these data point toward a familial aggregation, it appears desirable to await the results of a prospective family study before arriving at conclusions. In addition, the presence of some environmental agent common to these families will have to be excluded convincingly before the increased familial incidence can be ascribed to genetic factors.

The genetic basis of this neonatal jaundice may be a gene defect, different from the mutant gene that is present in the majority of G6PD-deficient people or a different expressivity of the same gene or an associated independent defect. But this is, as yet, a matter of speculation. It will therefore be interesting to learn whether in other G6PD-deficient populations this type of neonatal jaundice is found with an incidence similar to that observed in Greece. Reports on various Negro populations and on the Jewish communities of Israel are therefore anticipated with great interest.

ALLISON: As Dr. Fessas said, a large number of cases have been described from Singapore, and a few from Sardinia. Evidence is accumulating that this condition exists also in West Africa. But, in contrast to this, this condition has not, so far as I know, been seen here at all, which is remarkable in view of the high incidence of G6PD deficiency in the Israel population. Dr. Szeinberg is going to tell us about that.

A. SZEINBERG

Some Remarks on Neonatal Risk in Jewish Communities with High Frequencies of G6PD Deficiency*

An enquiry among the pediatricians in several hospitals in this country did not disclose any awareness of differences in the frequency of neonatal hemolytic jaundice between the Ashkenazim and the various Oriental Jewish communities among whom the enzyme deficiency is very frequent. However, in view of the

* The investigations reported in this presentation were supported by grants from the U.S. National Institutes of Health (A 2740) and from the Rockefeller Foundation (RF 60101).

reports from Singapore, Greece, and Sardinia,[1-5] we decided to investigate this problem more closely. This investigation has been carried out mainly by Dr. Oliver.

The first approach was the study of some villages in which the Kurdish Jews were concentrated. As has been pointed out before, the village of Maoz Zion in the Jerusalem mountains is inhabited by Kurdish Jews with about 70 percent enzyme-deficient males. During the last 3 years, 203 live infants were born in this village, all of them delivered in well-established hospitals in Jerusalem with good documentation of the clinical histories of the patients. It is possible to calculate that among these 203 children there were about 70 enzyme-deficient males, 50 enzyme-deficient homozygous females, and about 40 heterozygous females. Dr. Fessas has told us that about 5 percent of the enzyme-deficient newborn in Greece undergo severe hemolytic crises. This means that we should have found about six similar

TABLE I
THE FREQUENCY OF G6PD DEFICIENCY AND EXCHANGE TRANSFUSIONS IN VILLAGES INHABITED BY KURDISH AND PERSIAN JEWS, 1957-1960

	Maoz Zion	*Noga*	
	Kurdish Jews	*Persian Jews*	*Kurdish Jews*
G6PD deficiency among males	70%	15%	35%
Number of live births	203	58	61
Cases of kernicterus	0	0	0
Cases of exchange transfusion	3*	0	0

* Possible cause of hemolysis: Rh incompatibility—1; ABO incompatibility—2 (sisters).

cases in the village (taking into account only the enzyme-deficient males and the homozygous females) if a similar mechanism operated in our population. Contrary to this expectation, not a single case of kernicterus has been recorded in the village during the investigated period and only three cases of severe hemolytic jaundice necessitating exchange transfusion have been encountered. In one of these cases Rh incompatibility and in the two others (two sisters) AO incompatibility have been proved (Table I).

The village of Noga (near the ancient Gat of the Philistines) is now inhabited by Kurdish Jews with 35-percent frequency of enzyme deficiency and by Persian Jews with 15-percent frequency among males. During the past 3 years, 112 babies were born (at the Kaplan Hospital in Rehovot). No case of kernicterus or of

1 Smith, G. D., and Vella, F., Erythrocyte enzyme deficiency in unexplained kernicterus, *Lancet, i*, 1960, 1133-1134.
2 Weatherall, D. J., Enzyme deficiency in haemolytic disease of the newborn, *Lancet, ii*, 1960, 835-837.
3 Panizon, F., Erythrocyte enzyme deficiency in unexplained kernicterus, *Lancet, ii*, 1960, 1093.
4 Panizon, F., L'ictère grave du nouveau-né associé à une déficience en glucose-6-phosphate déhydrogénase. *Biol. Neon., 2*, 1960, 167-177.
5 Doxiades, S. A., Fessas, Ph., and Valaes, T., Glucose-6-Phosphate Dehydrogenase deficiency. A new aetiological factor of severe neonatal jaundice, *Lancet, i*, 1961, 297-301.

exchange transfusion was recorded. The examination of the hospital records showed that in 44 percent of these infants jaundice was observed. This is quite a high figure, and we thought that it could point to a particularly high incidence of jaundice among these children. However, in a control group of 200 consecutive births from all communities in the same hospital, jaundice was recorded in 53 percent. This implies that the physicians of this hospital were "jaundice-conscious" and recorded every slight case (physiological jaundice).

As the number of investigated newborn in these villages was small and the possibility of chance findings was high, we tried an approach which could be based on larger figures. Using the information available at the Kaplan Hospital in Rehovot, we compared the frequencies of exchange transfusions in population groups differing widely in the frequency of enzyme deficiency. During the past 4 years about 12,000 births have been registered at this hospital and 44 exchange

TABLE II
THE DISTRIBUTION OF EXCHANGE TRANSFUSIONS AMONG JEWISH COMMUNITIES WITH DIFFERENT FREQUENCIES OF G6PD DEFICIENCY, 1957-1961

Origin of parents	*Total live births*		*Exchange transfusions**		
	No.	*%*	*Rh incomp.*	*ABO incomp.*	*No incomp.*
Iraq, Iran, and Kurdistan	1661	16	2	5	1
North Africa	4052	39	2	11	1
Yemen	1407	13	3	1	2
Other Oriental & Sephardic	822	8	—	—	—
Ashkenazic	2512	24	6	9	1
Total of known origin	10454	100			
Unknown	1935		—	—	—
Total	12389		13	26	5

* G6PD-deficient babies among cases of exchange transfusions:
Iraqi (ABO Incomp.): 2
Kurdish (No Incomp.): 1
Total 3

transfusions were performed (13 cases with Rh incompatibility, 26 with ABO incompatibility, and 5 without incompatibility—Table II). The ethnic distribution of the cases that were not due to Rh incompatibility was in good agreement with that of all the inmates of the maternity ward at the same period. A statistical analysis showed homogeneity of the whole polulation with respect to the exchange transfusions not due to Rh incompatibility. There were only three enzyme-deficient babies (two Iraqi and one Kurdish) among those requiring exchange transfusion.

These investigations, which are being continued, suggest that in our population G6PD deficiency does not play a significant role in hemolytic incidents in the newborn. Of course, the investigated sample was small, and the possibility of future occasional findings of this type of hemolysis could not be excluded. The fact, however, that such cases seem to constitute a very significant proportion of

exchange transfusions or kernicterus in Malaya or Greece, where the enzyme deficiency is much rarer, points to a possible difference between the respective populations. Different loci or alleles for G6PD deficiency, modifiers, or environmental factors may jointly or separately be responsible for such an effect. It is possible, for example, that some food taken by the mothers or concurrent infections in mother and child could contribute to the development of the neonatal hemolysis in the other countries but were not operating under Israeli conditions.

In spite of this conclusion, we should remember, in all fairness, that our investigation was conducted in Israel, where these people were newcomers, and not in the countries in which they had lived for generations. We cannot exclude the possibility that in those countries conditions precipitating hemolysis of the newborn existed and influenced the establishment of a balanced polymorphism. However, the fact that in northern Kurdistan the frequency of the enzyme deficiency among Jews reached 70 percent militates against the conclusion that it had a significant detrimental effect.

GOLDSCHMIDT: I would like to add a few comments on selection and drift for G6PD deficiency in the Kurdish Jews. When, 3 years ago, Dr. Cohen and Dr. Bloch started their viability studies of this group, Dr. Matoth[1] had already drawn attention to their considerable thalassemia rate. We felt that the concentration of enzyme deficiency in this population and the physiological interaction of this trait with the anemia deserved interest. We found 80 percent of their X chromosomes carrying the gene for the enzyme deficiency, and we also noted a favorable interaction between the two erythrocyte defects[2] (see also p. 274).

This appeared to be a singular case of a population in which a "defective" gene had almost completely replaced the normal allele, and of course we looked for viability effects. The medical files of our immigrant village contained reports on all individuals over the past 8 years. Not a single recorded case of childhood death could be ascribed to hemolysis. Among the children of the village—numbering 620 in 1958—during the 8-year period there had been four transient hemolytic attacks. Among 400 recorded births there had been only three cases requiring exchange transfusions, and all three were stated to be due to ABO incompatibility. The serological data on this alleged incompatibility were fragmentary, and such cases may require further study.

In the four hamlets in the Kurdish mountains where these people lived before their immigration to Israel, medical care had been poor and infant mortality extremely high. The hearsay information gave no clue to the frequency of deaths from either hemolysis or malaria.

1 Matoth, Y., Shamir, Z., and Freundlich, E., Thalassemia in Jews from Kurdistan, *Blood, 10,* 1955, 176-189.

2 Cohen, T., Goldschmidt, E., Adam, A., Matoth, Y., Theodor, E., and Szabo, M. A., The frequency of rheumatic heart disease, glutathione instability and thalassemia in children of Kurdish Jews, *Harefuah, 57,* 233-236.

At first we suspected that the excessive accumulation of the mutant gene could be traced to one of the four villages. We mapped the distribution of the unaffected X chromosomes according to the birthplaces of parents and grandparents and it turned out to be fairly homogeneous over the area. Only a few of the normal genes had been recently introduced by intermarriage with Kurdish Jews from more distant localities. Nevertheless, it is possible that the Jews of the four hamlets were a "pure" enzyme-deficient population some while ago and that the normal genes have been imported.

In recent generations the Jewish population of this area was apparently too large to be subjected to dramatic drift. After World War II the number of Kurdish Jews in northern Iraq was estimated at 15,000 to 18,000.[3] A constant gene flow was maintained between this group and the Kurdish Jews of Persia and Central Turkey (see p. 345).

In view of the tendency to cousin marriages, prevailing to this day, it could also be suggested that this population was virtually split up into a series of smaller breeding units or clans. The present marriage pattern gives only little evidence of such a compound population structure. Today the children of first cousins are equally liable to marry again into the family or to choose an unrelated partner (see p. 347). This may have been different in the past. At all events, a compound population model fails to answer the problem, because a set of small isolates should not drift in the same direction.

It is much more likely that the Jews of this area stem from a few ancestral individuals, possibly from the survivors of a catastrophe of which no historical records are preserved. If we reject this hypothesis of drift, we are left with the alternative that selection was solely responsible for the accumulation of the defective gene. This would imply that the adaptive value of enzyme-deficient subjects in Kurdistan was far superior to that of normals and also to that of trait carriers in Sardinia and Africa.

ALLISON: In addition to the disadvantage which seems to exist, at least in some regions, to the newborn children with the trait, it is, of course, well known that favism is a serious disease in some parts of the world. It is possible that various environmental agents such as bacterial and virus infections—which in certain circumstances appear to produce hemolysis in these subjects—would also produce natural selection against this trait. Hence we have abundant evidence that all the traits we have been considering are disadvantageous under certain conditions, despite which they persist in high frequencies in some regions. It is therefore most plausible that the heterozygotes may enjoy an advantage under certain conditions. Now, this was shown, first of all, for the sickle-cell trait. The evidence on protection against malaria is so well known that I think it need not be discussed in detail here. But Dr. Motulsky is going to tell us about the possibility that a similar protection is also conferred by G6PD deficiency.

3 Ben-Jacob, A., *Kurdistan Jewish Communities*, Ben-Zwi Institute, Hebrew University, Jerusalem, 1961.

MOTULSKY: Some three years ago we were struck by the correlation between the geographic distribution of G6PD deficiency and falciparum malaria. This correlation appeared to indicate that the malaria hypothesis may apply to the enzyme deficiency as well as to the sickle-cell trait. This type of evidence is merely circumstantial, but some additional proofs have actually come forth in field surveys carried out in various areas.

Dr. Siniscalco has reported on the field studies that he and I have done with his group in Sardinia. In the coastal areas, where endemic malaria had only recently been wiped out, the trait frequency was high, whereas in the populations of the central mountains, where malaria had been absent, it was quite low. It is important to point out that the populations of the coastal and the central regions were very similar by blood-group distribution. The argument for selective agencies being responsible for the variation in the concentration of the trait in Sardinia is therefore quite strong.

Similar proof has recently been adduced from New Guinea and New Britain by Dr. Kidson. In mountainous regions of New Guinea he found no G6PD deficiency, whereas in New Britain, in an otherwise similar population, the incidence ranged from 12 to 15 percent.

Since we know that the sickle-cell trait is selected for by malaria, a correlation between the frequencies of sickle-cell trait and enzyme deficiency may also tend to show that both mutant genes are favored by the presence of the same ecological agent. Such a correlation has been found in Congo populations studied by Dr. Vandepitte and me 2½ years ago. Dr. Allison accumulated data on a number of other African tribes, and the combined results show a remarkable correlation between the two erythrocyte defects.

In Sardinia, where G6PD deficiency occurs in conjunction with thalassemia instead of Hb S, there was a parallel situation, the enzyme deficiency being common in populations with higher frequencies of thalassemia. However, at higher frequencies of G6PD deficiency the thalassemia rate levels off, apparently because it cannot reach very high frequencies, being lethal in homozygotes. It is interesting that in Kurdish Jews who have reached such a high level of G6PD deficiency, thalassemia appears to be about as common as in Sardinian populations (see also p. 272).

More direct evidence has been produced by parasite counts and by observing the course of malaria attacks in enzyme-deficient subjects. When we were in the Congo 2½ years ago, we tried to show an effect of the enzyme deficiency and of sickling as a control on parasite rate. As you know, there is a correlation between mortality from malaria and the density of the parasites: the larger the number of parasites in the red cells, the higher the mortality from malaria. This type of study presents technical difficulties, because one has to be very careful to select age groups devoid of acquired immunity to malaria. Children in a malarial environment are born with a passive immunity from their mothers which disappears after a few months.

Then, during the next few years of life, these children acquire active immunity against malaria, which may blur any effect of genetic protection by the erythrocyte mutants. Unfortunately, in the hope that the acquired immunity would not be complete in children below 10 years of age, we chose for various reasons children who were for the most part between 5 and 10 years of age.

Although the mean parasite count was a little lower in the enzyme-deficient children, this is not statistically significant. Dr. Allison has done similar studies in Tanganyika on children below 4 years of age and actually has demonstrated lower parasite counts among male enzyme-deficient children in that area, and in sickling children, than in normal controls.

Another study has been done in Siam, where the frequency of the enzyme-deficiency trait is 15 percent. Unfortunately, the investigator did not classify the types of malaria in his material. About 60 to 70 percent of his malaria is vivax malaria, and in a population of several hundred boys between 1 and 3 years of age he was unable to show any difference in parasite counts between enzyme-deficient and normal children. So this is where the direct evidence stands.

There are some other, more fragmentary data about malaria incidence in enzyme-deficient subjects. When he last wrote to me a few months ago, Dr. Gilles, in Nigeria, had seen 23 children with severe cerebral falciparum malaria Since the incidence of the trait is 20 percent in that area, he might have expected to find four or five enzyme-deficient children in this group, but he has not found any. Similarly, in Gambia, among 31 children who were followed by malariologists there very carefully, there were three enzyme-deficient children. These children had briefer periods of parasitemia, and two children in this group who were judged to be less severely affected than the rest were both enzyme deficient. Certainly, these data are few, and many more are necessary.

In summary, then, the evidence for the malaria hypothesis in relation to G6PD deficiency is mostly indirect and based on geographic distribution. The general geographic distribution is in good agreement with the hypothesis and so is the regional distribution mapped in certain areas, such as Sardinia and some African states.

Additional arguments concern the correlation of the enzyme deficiency with the sickle-cell trait in a beautiful straight line and its correlation with thalassemia in a pretty good manner. More data on parasite density are certainly needed, and the information on actual disease incidence in trait carriers is most fragmentary. Nevertheless, I should be greatly surprised if this hypothesis were to be disproved in the future.

ALLISON: In this connection I should just mention two points which some people who do not have much experience with malaria may be unaware of. The age effect which Dr. Motulsky mentioned is very important. In a region where one is dealing with hyperendemic malaria, there is extremely high immunity above the age of about 5 and parasite counts may be very low. It is therefore very difficult

to show any protection in the older age groups, as has become quite clear in the case of the sickle-cell trait. Although there is abundant evidence that this protection operates in younger children, there is also good evidence that it does not operate at ages beyond about 5 years.

For this reason, among others, I was inclined to think that the protection against malaria operated by a mechanism of differential survival. It may be assumed that children with the sickle-cell trait will stand a better chance of surviving through the dangerous years of first exposure to the disease than children without the trait, and for this reason you will have a higher proportion of sickle-cell trait carriers of reproductive ages than in the population of the newborn. And I think the evidence, so far as it goes, quite strongly supports this hypothesis.

Dr. Neel would like to add a remark.

NEEL: As Dr. Motulsky has mentioned, my colleagues and I have emphasized in several reviews the growing evidence that there is actually selection against the individual with the sickle-cell trait. In other words, selection may operate against the heterozygous individual. We have also emphasized in the past that there is evidence of selection against thalassemia minor, the heterozygote for the thalassemia gene. After all, these individuals average two gm. of hemoglobin less than normal, and this can scarcely be an advantage at a time of blood loss.

We have just heard a review of the rapidly accumulating evidence that, in addition to the well-known susceptibility to favism, G6PD deficiency is also associated with jaundice in the newborn. Now, this means that for these various mutant genes to achieve the frequencies which they have achieved, the agent of selection must, indeed, be a very powerful agent. It must not only be enough to offset the loss of homozygotes through sickle-cell anemia or thalassemia major, as the case may be, but in addition to offset the occasional gene loss due to selection against the heterozygote. It is truly remarkable that we have had the good fortune to come upon situations in which a single gene can confer such a marked survival advantage in a particular circumstance.

I think it is quite obvious that a polymorphism of this nature is a rather wasteful polymorphism, that this protection against malaria is achieved at the cost of a good many deaths from sickle-cell anemia plus whatever deaths result from the sickle-cell trait. On an intuitive basis, we are entitled to suspect that these may be rather recent polymorphisms which in time would be superseded by less wasteful polymorphisms. There is another corollary we can suspect: that if there is indeed selection against the heterozygote, then genetic drift is relatively unimportant in connection with genes such as the sickle-cell trait or thalassemia.

Now, with respect to the antiquity of this polymorphism, some recent data from Africa are rather pertinent. It has already been mentioned that off the northwestern tip of Ghana, in Upper Volta, is the highest concentration of the hemoglobin C trait which has yet been reported. There is also a high frequency of the sickle-cell trait in this region. There has been quite a bit of discussion as to whether

in this area of overlap between high frequencies of hemoglobin C and hemoglobin S, the genes concerned are in an equilibrium situation. This is a debate which rapidly gets quite technical and can be deferred for the present.

However, there are other areas in West Africa where there is no debate about it, where the populations are indeed very far from equilibrium. This is the situation I want to describe now. Liberia is a small country in West Africa, some 300 miles long and 150 miles wide. Some five years ago, when we undertook studies on the hemoglobinopathies of this region, there quickly came to light a rather unexpected situation. When the studies were projected for Liberia, it was anticipated that the frequency of the sickle-cell trait would be rather high. In point of fact, it was discovered that in the northwestern tip of Liberia the frequency of the sickle-cell trait was about 20 percent. As one proceeds to the east and to the south, the frequency of the sickle-cell trait falls in a very striking cline, until at the southeast corner the frequency of the trait is 1 percent.[1, 2] This is one of the most striking gene clines that we have yet come upon in human genetics. As one proceeds toward Ghana to the east, the frequency of the sickle-cell trait rises very rapidly. Hemoglobin C is almost absent in the tribes of Liberia.[3] Now, how can this be interpreted?

There are reasons for regarding the tribes of Liberia and of the immediately adjacent Ivory Coast as having many Paleo-Negroid characteristics. These tribes appear to have been compressed into this rather undesirable part of West Africa by their more successful neighbors to the north, and one can speculate that at the time they were driven into this area, the sickle-cell gene was not yet present in any frequency.

Now, to come back to the malaria story. Malaria has probably achieved its present medical importance only with the introduction of agriculture and the consequences which follow—namely, the clearing of the land and the increase of the human population to a point at which it becomes an important food source for mosquitoes. And it is a fact that the agricultural revolution reached certain parts of West Africa not very long ago.

Accordingly, it is an interesting speculation that in West Africa the introduction of agriculture, and with it the conditions which result in the build-up of malaria pressures, are of relatively recent occurrence; close behind malaria comes the genetic mechanism that will help the population with a partial immunity to this disease.[4]

1 Livingstone, F. B., The distribution of the sickle-cell gene in Liberia, *Am. J. Human Gen., 10,* 1958, 33-41.

2 Livingstone, F. B., Anthropological implications of sickle-cell gene distribution in West Africa, *Am. Anthrop., 60,* 1958, 533-562.

3 Neel, J. V., Hiernaux, J., Linhard, J., Robinson, A., Zuelzer, W. W., and Livingstone, F. B., Data on the occurrence of hemoglobin C and other abnormal hemoglobins in some African populations, *Am. J. Human Gen., 8,* 1956, 138-150.

4 See Livingstone, Anthropological implications of sickle-cell gene distribution in West Africa, *loc. cit.*

ALLISON: An additional point has been raised, particularly by Dr. Livingstone, who suggests that there may also be an important differential-fertility effect—that is to say, under malarious conditions women with the sickle-cell trait will be more fertile. They will be less inclined to have abortions and will tend to produce a higher proportion of live-born children than women without the trait.

Some pertinent evidence has recently been produced by Dr. Firschein in British Honduras[1] and also by Dr. Roberts in West Africa. I wonder whether Dr. Roberts would care to comment on this selective mechanism.

ROBERTS: Cross-sectional studies of the incidence of electrophoretically determined hemoglobin types in Yoruba children appeared to show that there was an increase in frequency of Hb^A/Hb^S and a diminution of Hb^A/Hb^A individuals between the ages of 4 months and 4 years, by which latter age adult frequencies were achieved.[1] We interpreted these trends as being due to differential mortality, but we were not sure that this was sufficient to maintain the hemoglobin gene frequencies in equilibrium. We then calculated the relative fitnesses of the genotypes for all West African samples for which frequencies of the Hb^A, Hb^S, and Hb^C genes were available, and we examined these in the light of the mathematical criteria for stability of a triple allelic system.

In only a minority of West African populations were the genotypic fitnesses adequate for the maintenance of a stable polymorphism. Because we wondered whether there entered into the balance some additional factor such as differential reproductive performance, we examined the reproductive success of 225 matings between different types of zygotes. Taking account of differences in the duration of marriage and of variations in the number of live births during the maternal reproductive period, we found that the average number of pregnancies per year of marriage between a heterozygote and a normal homozygote was .41, whereas in unions between normal homozygotes it was .39. Apparent differences in the proportion of miscarriages reduced the differential in number of live births per year of marriage. The reproductive performance of the union between the heterozygote and the normal homozygote also depended on whether the father or the mother was the trait carrier. However, the net effect of all these differentials was to produce a very slight increase in the frequency of the Hb^S gene in the next generation.[2] Incidentally, from these reproductive histories for our own particular sample we were able to calculate the probability of death for a child of a given genotype. We could show from the ages at death of offspring in various unions that normal homozygous children suffer greater mortality earlier in life than

1 Firschein, I. L., Population dynamics of the sickle-cell trait in the Black Caribs of British Honduras, Central America, *Am. J. Human Gen., 13,* 1961, 233-254.

1 Roberts, D. F., and Boyo, A. E., Abnormal haemoglobins in childhood among the Yoruba, *Human Biol.,* 1961. In press.

2 Roberts, D. F., and Boyo, A. E., On the stability of haemoglobin gene frequencies in West Africa, *Ann. Human Gen 24,* 1960, 375-387.

heterozygotes, and we could thus confirm the age trends I mentioned at the beginning. This work cannot yet, of course, be regarded as completed.

ALLISON: I think I ought to stress at this point that general conclusions must not be drawn from observations relating to a particular parasite species. It is quite likely that *Plasmodium vivax* will behave differently from *Plasmodium falciparum* in this respect, if only because vivax parasitizes selectively young cells with high enzyme activity.

It is also worth mentioning that there are good biochemical reasons why enzyme-deficient subjects might be able to support the growth of malaria parasites less well than individuals with normal enzymes. The chief reason is that the malaria parasite seems to require reduced glutathione for multiplication, as studies of growth of parasites in hemolysates show. It is also known that a high proportion of the sulfur requirements of the parasites are met by cysteine in the cell. Hence, if the mechanism for reduction of glutathione in the cell is impaired, as it may well be in the enzyme-deficient cell, one would expect the parasites to grow less well. However, these data are tentative at present, as Dr. Motulsky has emphasized, and there are various things which should be done in order to establish this hypothesis on a firm basis. I know Dr. Sheba has views on this matter which I hope he will present now.

CH. SHEBA

Environmental vs. Ethnic Factors Determining the Frequency of G6PD Deficiency*

It has been stated here and in all publications referring to the matter that there has to be a selective advantage of enzyme deficiency with regard to death from falciparum malaria—in line with the idea advanced long ago by Prof. Haldane with reference to thalassemia, and brilliantly investigated by Dr. Allison. Evidence has been produced, partly on a statistical basis and partly by direct investigations, that enzyme-deficient red cells, being a poor medium for multiplication of plasmodia, confer an advantage in case of malaria infection. I think that one has to pose a number of questions to those who advocate such a possibility. In the following presentation I shall ask these questions, and I should like to point out some facts which need further study.

Let me turn first to geography. If one speaks broadly of malarial areas, one may

* These investigations were supported by Grant A-2740 from the U.S. National Institutes of Health and Grant RF-60101 from the Rockefeller Foundation.

commit errors. In his book, *Malaria in Europe*,[1] Hackett pointed out that in Ceylon, with stream-breeding Anophelines, malaria will occur in the hills, whereas in India, with stagnant-water breeders, malaria will occur in the valleys. It took a long time to discover this. Now, in the areas with the highest incidence of enzyme deficiency, such as Kurdistan or the Caucasus Mountains, one is dealing with high mountain villages. I tried to get information from the late Prof. Mer and from Dr. Joffe, who worked with him, on whether stream breeders are most responsible for malaria in Kurdistan. Except for *Anopheles claviger*, which is both a stream breeder and a vector of malaria, this does not seem to be the case. If compared with the malaria map of the area (see p. 275), the data produced by Cohen *et al.* (see p. 272) on the incidence of very high enzyme deficiency in certain Kurdish villages do not support the geographic coincidence invoked.

Now, if we assume that malaria was responsible for the high concentration of this mutant gene in Kurdistan, one may legitimately ask why the whole North African coast should present such a low concentration of enzyme deficiency—*i.e.*, around 1 percent. In addition, we know that in Iraq, Baghdad-Spring-Anemia was very common in Jewish boys and very rare in Moslems.[2] We were also told by our colleagues who came to this country from Iraq that favism, apparently identical with Baghdad-Spring-Anemia, was mainly a disease of the Jewish minority in that country. It is strange that a difference in the frequency of G6PD deficiency, possibly as wide as that existing between the Ashkenazic and the Iraqi Jews, should have occurred in Iraq in two populations exposed to the same environment for about a hundred generations.

There is one more point concerning the geographic distribution of this trait: in Ethiopia, Mr. Adam and Miss Bat-Miriam[3] found enzyme deficiency to be absent not only in the Fallasha, the Jews of Ethiopia, but also in the Ethiopians proper. More than 800 males have been examined. It is also of interest that no abnormal hemoglobins have been found in these 800 bloods studied by Dr. Lehmann in London. In general terms, Ethiopia may be called a malarial country (although we performed our studies at above 1000 meters). Thus, a country in Africa was found to be free of sickle-cell trait, of G6PD deficiency, and of thalassemia.

If one now turns to the direct evidence, the parasite count, and to the information mentioned by Dr. Motulsky concerning the children in Ghana, to the best of my knowledge only the Motulsky test is being performed there and the children are examined at the height of their disease, when there can be as much as 50 percent of young red blood cells. I do not know whether the absence of enzyme deficiency in such circumstances in a sample of any size, let alone a small one, could be taken

1 Hackett, L. W., *Malaria in Europe*, Oxford University Press, 1937, 232 pp.

2 Lederer, R., A new form of acute haemolytic anaemia, "Baghdad Spring Anaemia," *Trans. Roy. Soc. Trop. Med. Hyg.*, *34* : 5, 1941, 387-394.

3 Adam, A., and Bat-Miriam, M., A survey of some genetic characters in Ethiopian tribes, Proceedings, Second International Conference on Human Genetics, 1961. In press.

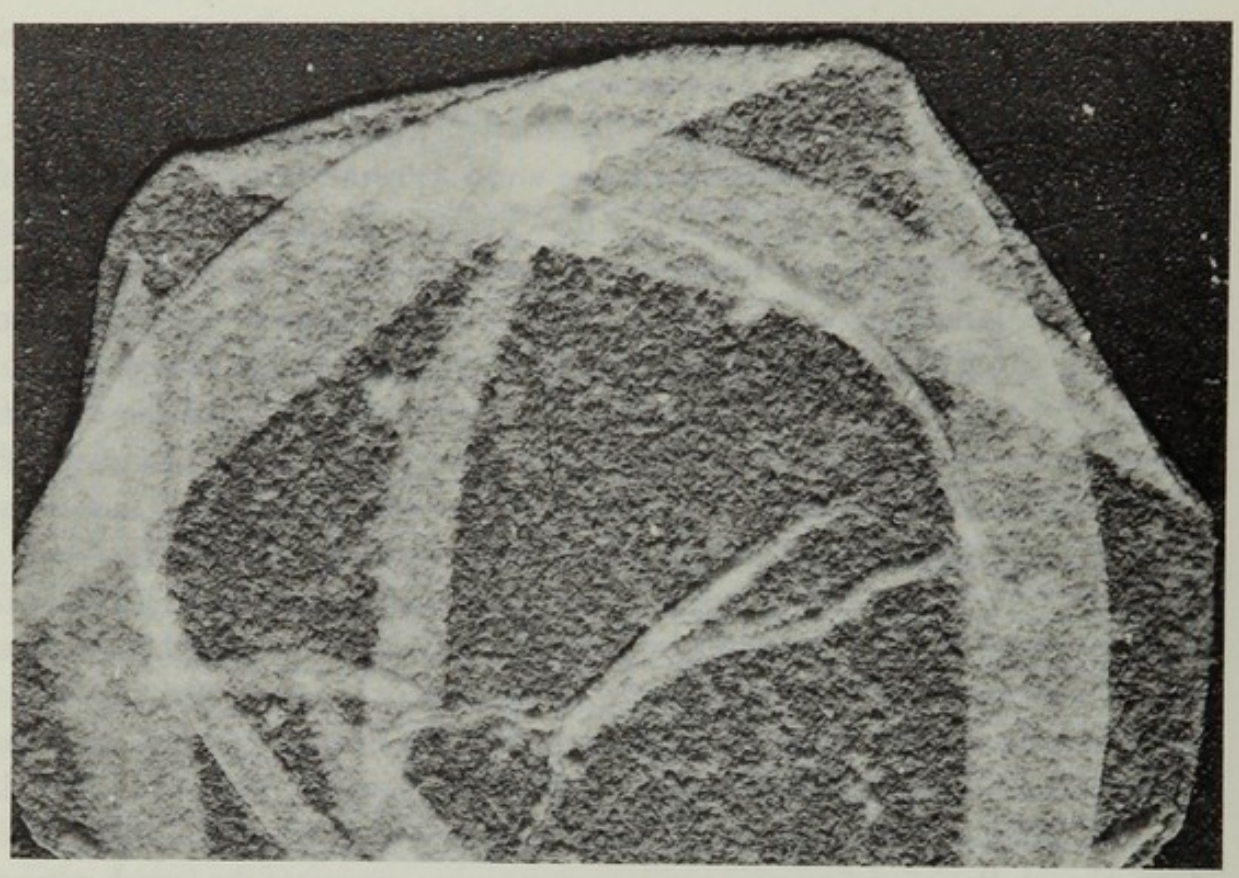


FIG. 20. Granular coarse membrane of young red blood cell (70-90% in normal individuals, 10-30% in enzyme-deficient individuals).

as evidence in favor of an advantage conferred by enzyme deficiency in the presence of malaria.

I should also like to remark on inferences based on parasite counts. Dr. Allison pointed out that the host and the parasite compete for glutathione, a view to which I subscribe. But if parasite counts are used as evidence of the severity of infection or, as Dr. Motulsky has said, as a rough yardstick for the risk of death from malaria, I would quote Dr. Adler, who maintains that in cases of severe blackwater fever from falciparum infection, one finds very few parasites in the peripheral blood. Thus here is an instance of death from falciparum malaria with a low parasite count. Obviously, the residual stroma plus the parasite are removed by the spleen and by the capillaries of other internal organs. In his first paper on this subject,[4] Dr. Motulsky assumed, I believe correctly, that falciparum parasites invade the small cells, which are the older ones. Therefore these cells, already past their prime, are destroyed in the presence of a competitor before their natural date of expiration.

Enzyme-normal and enzyme-deficient individuals appear to differ from each other quantitatively in the composition of their red-cell population with regard to content of enzyme and glutathione and the stability of the latter. We have tried to illustrate this with Dr. Danon of the Weizmann Institute using the electron

[4] Motulsky, A. G., Metabolic polymorphisms and the role of infectious diseases in human evolution *Human Biol., 32,* 1960 28-62.

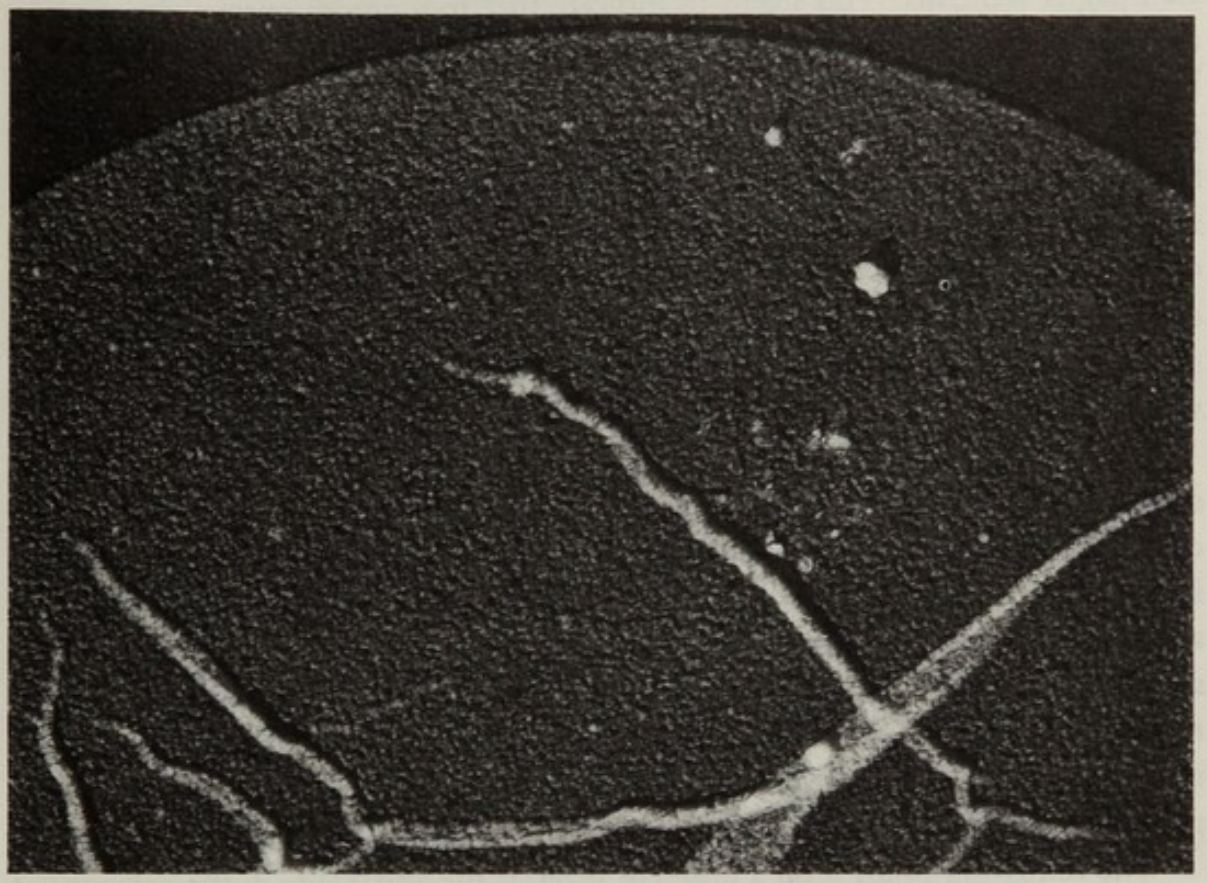


FIG. 21. Smooth membrane of old red blood cell (10-30% in normal individuals, 70-90% in enzyme-deficient individuals).

microscope.[5] Young cells (Fig. 20) show a very granular surface and a considerable thickness as compared with old cells, which are much thinner, as can be seen from the shadows they cast (Fig. 21), and have a very fine surface granulation. Enzyme-deficient individuals have a majority of the latter type of cell, which is by our definition prematurely senescent. In some cases they possess up to 90 percent of this type and only 10 percent of the thick, granular "young" cells; in enzyme-normal individuals the ratio is reversed. A reversal also occurs in an enzyme-deficient person after severe hemolysis following the administration of sulfapyridine or a meal of fava beans. In other words, enzyme-deficient individuals have a majority of cells which, if invaded by a parasite, will take only a very short time to exhaust their glutathione and subsequently to undergo destruction.

Since I assume that in the competition between parasite and host the former usually wins, I have difficulty in accepting the opposite view. There may be another possibility—namely, that enzyme-deficient individuals are less attractive to mosquitoes. It is known that to some Anophelines certain animals are more attractive than humans, and vice versa. As an example I would quote Celli,[6] who maintains that pigs were considered a good protection against Anophelines in the

5 Danon D., Sheba, Ch., Ramot, B., The morphology of glucose-6-phosphate-dehydrogenase deficient erythrocytes: electromicroscopic studies *Blood, 17,* 1961 229.

6 Celli, A., Die Malaria nach den neuesten Forschungen, as quoted by Hackett (see footnote 1).

Campagna Romana. This seems to indicate that mosquitoes select their victims, and, for other concomitant reasons, it is possible that they are able to distinguish between enzyme-deficient and enzyme-normal individuals. Unfortunately, employing Aedes instead of Anopheles, we failed to prove this hypothesis. With the help of Miss Bath-Miriam, we tried two methods—*i.e.*, feeding the mosquitoes on normal and mutant individuals and putting a drop of blood on a membrane on top of a jar in order to determine whether the mosquito would distinguish between enzyme-deficient and normal blood. Our efforts in this respect should be disregarded, and similar experiments with Anophelines should be tried in countries in which malaria still prevails.

When estimating susceptibility of red cells to infection on the basis of parasite counts, one must remember to count only parasites that reside inside intact red cells. If such a red cell, invaded by a parasite, is prematurely destroyed because of its lower content of protective glutathione, the residual stroma plus the parasite are instantaneously removed into the spleen and into the reticulo-endothelial system at large. It appears indicated, therefore—again in countries in which malaria still prevails—that parasite counts together with red-cell counts should be made and that spleen rates vs. parasite rates should be studied. It may be that lower parasite counts could be found in those children who have lower red-cell counts.

The following point is on a different level. If the advantage in the presence of malaria concerns the heterozygotes, and if the homozygotes are at a disadvantage, being enzyme-deficient, the result would be a population with a selective advantage of one sex over the other. Is this a valid point, Dr. Allison?

For all these reasons and also to gain a better understanding of the differences between the Jews and the Moslems in Baghdad or between the Jews and the Circassians in the Caucasus Mountains, I tried to explain (I admit my colleagues hesitated) the selective occurrence of enzyme deficiency by ethnic origin, consanguineous marriage, and drift. An occasional enzyme-deficient person in England, preferably in Cornwall, could plausibly be of Phoenician stock. Dr. Jandel, of Boston, remarked during a discussion that in the Channel Islands there are cows that have hemoglobin abnormalities found also in cattle from Mediterranean islands but existing neither in France nor in England. Apparently the Phoenicians took cattle with them on their migrations. One even finds hemoglobin H in Sweden, and we know that this abnormal hemoglobin is due to a mutation existing mainly in the thalassemia belt. Therefore, when we learned that Kurdish and Iraqi Jews, in contradistinction to Ashkenazim, have a high incidence of enzyme deficiency, the same being true of Sardinians as against Italians, we were tempted to turn to history to find out whether there was any clue to a common origin of the groups distinguished by high frequencies of the mutant gene.

If you remember the Punic Empire, with its capital in present-day Bizerte (Carthage of those days), with bridgeheads to Rome in Sardinia but also with bases in western Sicily, Malta, and Minorca, and with agricultural settlements along the North African coast and the east coast of Spain, you will also understand

why Hannibal took this route when he planned to capture Rome. Along this line of communication he had a chain of posts for both reinforcements and supplies. Interestingly enough, this coastline has yielded many archeological finds of Hebrew inscriptions on clay plates, which provide evidence that a Hebrew population followed the same route as the Phoenicians (Fig. 22) or replaced them.[7]

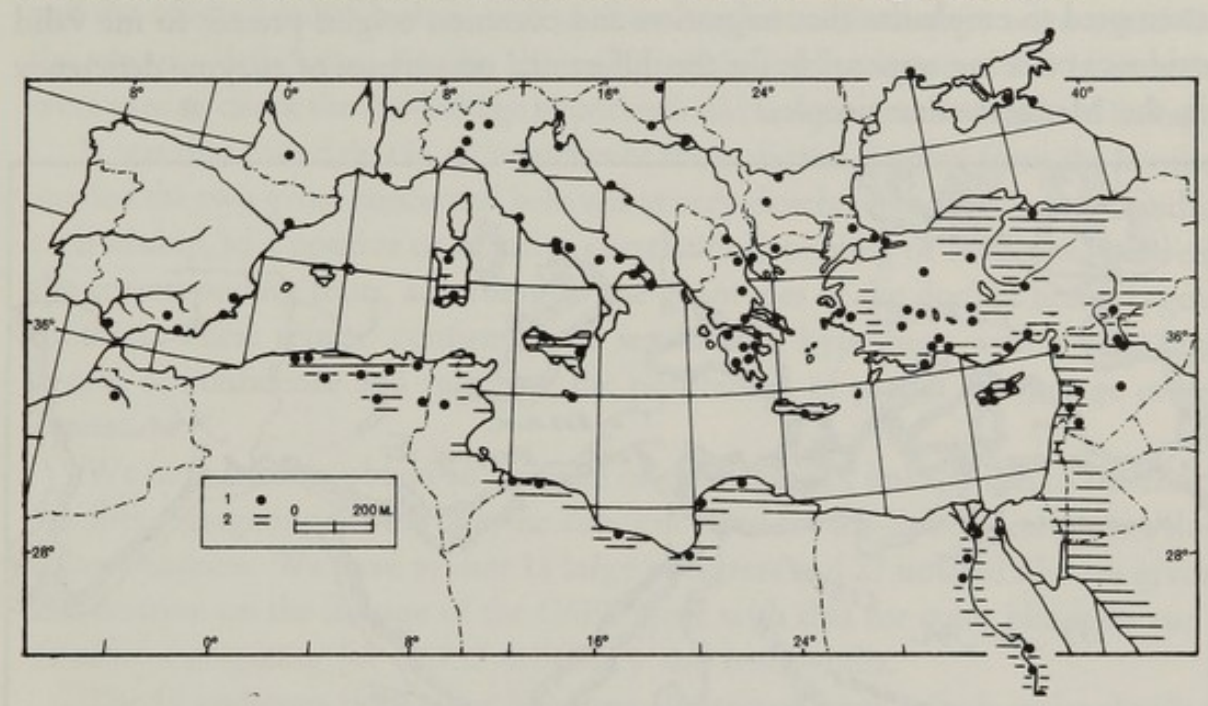


FIG. 22. The Jewish Diaspora of the early Christian centuries. •: Cities with large Jewish populations before the Fourth Century A.D. (so far as known). =: Dense Jewish rural settlement before the Fourth Century A.D. (so far as known). Redrawn from E. Isaac (see footnote 7).

We felt, therefore, that the Kurdish Jews, a concentrate of the ancient Hebrews exiled to Babylon, and the Sardinians and other Mediterranean islanders who were Punes (Phoenicians) could have a common origin and that on this assumption we would be able to explain at least why Sardinians should be so much more affected by favism than the Italians proper.

When you look at the geographic distribution of enzyme deficiency (see map on p. 271) in the Jewish communities available to our screening, you will notice that the area of highest concentration of enzyme-deficient individuals coincides with Mesopotamia. By the way, Mesopotamia is assumed to be the mother country of the fava bean,[8] and apparently it was banned from there, for its name in the old writings was the "Egyptian Bean."

The Yemenites, though far removed from the Mesopotamian group, to which the Persian Jews also belong, have a higher frequency of this trait than the North African Jews, and the Jews in Turkey also show a higher incidence of the trait than North African Jews, because Turkey represented an area of migration from Kurdistan.

Figure 23 takes us back to Prof. Haldane's quotes from old writings—not back

7 Isaac, E., Influence of religion on the spread of citrus, *Science, 129*, 1959, 179.
8 Personal communication from I. Glomnitzky of the Faculty of Agriculture, Rehovoth.

to David but, at least, to Josephus Flavius. It represents his concept of the division of the world among the three sons of Noah. Europe went to the sons of Japheth, in whom we see virtually no enzyme deficiency or hemoglobinopathy, the thalassemia belt went to Shem, and the sickle-cell belt went to Ham. Excuse my diversion—I was challenged by Dr. Motulsky to present some of this material. I have attempted to emphasize that migration and common origins present to me valid evidence of being responsible for the differential occurrence of enzyme deficiency in the Mediterranean peoples.

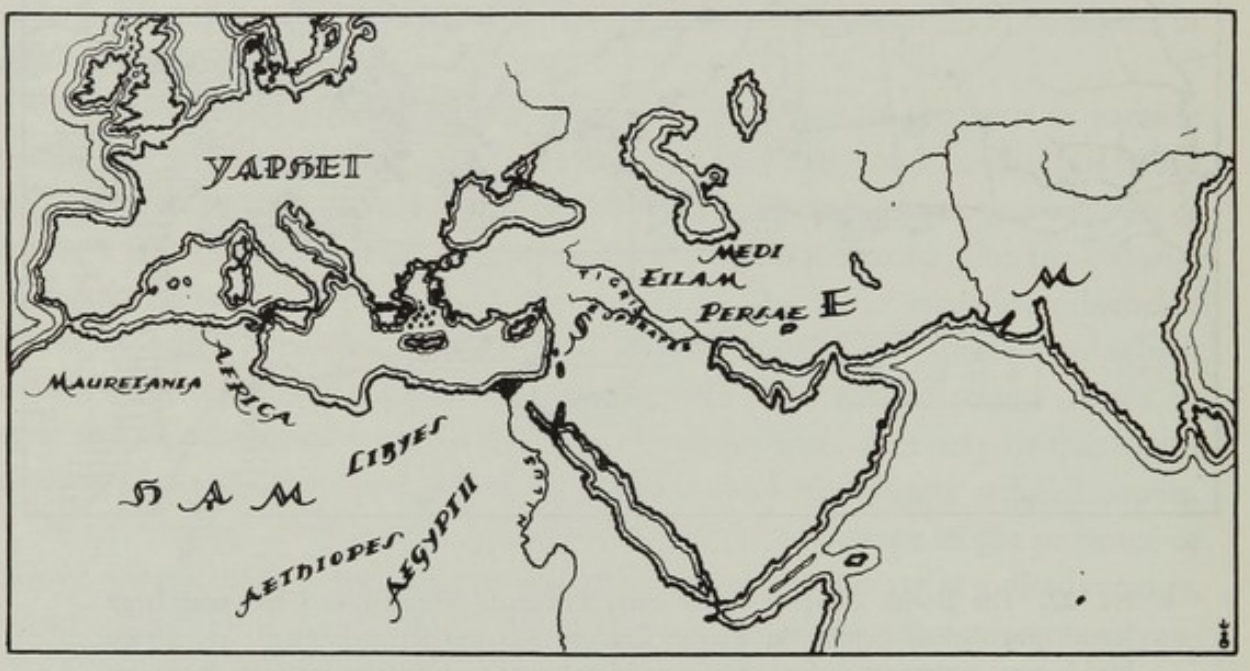


FIG. 23. Division of the world among Noah's sons as seen by Josephus Flavius.

ALLISON: One of the questions which Dr. Sheba has raised is whether the gene that is found in Sardinia is the same as the one that occurs here. It is possible that the linkage between G6PD deficiency and color blindness may have a bearing on this problem. Dr. Siniscalco will now report on his linkage studies in Sardinia.

M. SINISCALCO

Linkage Data for G6PD Deficiency in Sardinian Villages

In the course of our population studies on favism and thalassemia in Sardinia to which I referred earlier in this session, we have been able to accumulate data on the linkage relationships between the gene for G6PD deficiency and those for color blindness and hemophilia.

These studies served in the first instance to substantiate the sex-linkage hypothesis put forward by Childs *et al.*[1] to explain the population and family distribution of the G6PD phenotypes in American Negroes. For this purpose the population of an isolated Sardinian village, where the frequency of the enzyme deficiency was known to be appreciable, was screened for color blindness with the Ishihara tables, and the affected individuals as well as their brothers and mothers were tested for the enzyme deficiency. Finally, the pedigrees found to segregate for both traits were used to check the sex-linkage hypothesis and to estimate the degree of linkage.

It was thus found that in all branches of the pedigrees derived from the families studied the two genes concerned behaved as very closely linked, giving rise, within each sibship, to a positive or negative correlation (coupling or repulsion) between the corresponding traits, according to the genotypes of the doubly heterozygous mothers. These results[2] confirmed the sex-linkage hypothesis with a very high degree of confidence and ruled out the possibilities of partial sex linkage or sex limitation.

We next tried to obtain an estimate of the degree of linkage and to search for families segregating for the enzyme deficiency and for sex-linked genes other than color blindness. We have to date 11 large pedigrees and 27 isolated sibships giving information on the linkage of the G6PD gene with that for color blindness and 3 families segregating for G6PD deficiency and hemophilia.

The 11 pedigrees with color blindness all derived from a single isolated village which was almost completely screened. The diagnosis of the G6PD phenotypes in these families was obtained by measuring the red-cell enzyme activities spectrophotometrically and applying a different discrimination threshold for the thalassemic patients. The color-vision defects were first detected by means of the Ishihara tables, and the diagnosis was completed (whenever possible) with the use of Farnsworth's dichotomic test and with Nagel's anomaloscope. In our experience these rather laborious methods of diagnosis were found very important for linkage studies. They tend to avoid, on the one hand, misclassification of the enzyme-deficient "intermediate" women in the presence of thalassemia, and, on the other hand, they serve to discriminate true cases of recombination from spurious ones due to the occurrence of two or more types of color blindness in the same family.

In Table I, summarizing the linkage data for G6PD deficiency and color blindness, it may be seen that the 11 pedigrees, comprising 33 informative sibships, appear to yield only 2 recombinants out of a total of 91 male offspring. We tend to regard these recombinants with some reserve because they were both found in the same sibship. If, however, they were true recombinants, the 5-percent level fiducial limits of the cross-over value would be 0.002 and 0.04.

1 Childs, B., Zinkham, W. H., Browne, E. A., Kimbro, E. L., and Torbert, J. V., A genetic study of a defect in glutathione metabolism of the erythrocyte. *Bull. Johns Hopkins Hosp., 102,* 1958, 21-37.

2 Siniscalco, M., Motulsky, A. G., Latte, B., and Bernini, L., Indagini genetiche sulla predisposizione al favismo—Dati familiari Associazione genica con il daltonismo, *R. Accad. Lincei,* Ser. VIII, fasc. 6, *28,* 1960, 1-7.

Table I calls for further comment. The excess of families in which the two defects are in coupling and the peculiarly frequent association of the enzyme deficiency with the severe defect of the deutan type should be noted. There are but two families segregating for G6PD deficiency and protanomaly, and one of these furnished the only example of repulsion found in the village under study. Of especial interest is the occurrence of a variety of color blindness that we have provisionally called "extreme deuteranopia," in the sense that it appears to involve a type of green blindness more severe than the common deuteranopia. This was always found associated with the enzyme deficiency and appeared as such in all

TABLE I

TYPES OF COLOR BLINDNESS AND THEIR ASSOCIATION WITH G6PD DEFICIENCY IN A SARDINIAN VILLAGE

POPULATION DATA			FAMILY DATA (based on 33 informative sibships of 11 pedigrees)	
	Types of color blindness among 180 unrelated males		*Association of types of color blindness with G6PD deficiency*	
Type	*Affected males*		*Coupling*	*Repulsion*
	No.	*Rate*		
Deuteranomaly	7	0.044	—	—
Deuteranopia	6	0.033	6	—
Extreme deuteranopia	3	0.007	3	—
Protanomaly	5	0.029	1	1
Protanopia	1	0.006	—	—
All types	22	0.125	10	1

Informative children

Non-cross-overs	Cross-overs
89	2

Cross-over value $2/91 = 0.022 \pm 0.015$

affected relatives of the propositi in three large and apparently unrelated pedigrees. We feel that these individuals could be carriers of a double defect (protan-deutan color blindness) although the involvement of a different allele at the deutan locus cannot be excluded. [Note added in proof: some of these patients examined in Geneva by Prof. A. Franceschetti and Prof. W. Jäger have been classified as "extreme deuteranopes."]

Table II shows that the excess of coupling exists also in other Sardinian villages. It is further relevant that three of our repulsion families (in the village Teulada) clearly derive from a mating between a Sardinian woman and a man born in an area of northern Italy where the G6PD deficiency is virtually absent. A similar explanation based on common origin may possibly apply to the excess of repulsion found by Dr. Adam (see p. 112) in 19 Israeli families which otherwise confirm the very close linkage between the two genes.

The excess of coupling is not the only peculiarity of the data shown in Table II. There is also a noticeable positive correlation between the frequency of color blindness and that of enzyme deficiency (see also Fig. 24). Finally, in most of the

villages studied thus far, the incidence of the enzyme deficiency among unrelated color-blind males appears to be higher than in the general population.

We have two working hypotheses to explain these data. The first postulates the existence of a selective mechanism of the type illustrated in Table III. This assumes

TABLE II

INCIDENCE OF G6PD DEFICIENCY AND COLOR BLINDNESS AMONG UNRELATED MALES OF 9 SARDINIAN VILLAGES*

	G6PD DEFICIENCY *g*			COLOR BLINDNESS *c*			INCIDENCE OF *g* AMONG *c*†		NUMBER OF FAMILIES GIVING INFORMATION FOR LINKAGE STUDIES	
Locality	*No. males investigated*	*Rate of affected*	*± ST.E.*	*No. males investigated*	*Rate of affected*	*± ST.E.*	*No. c males investigated*	*Rate of g*	*Coupling*‡	*Repulsion*
Cabras	200	0.35	0.03	250	0.115	0.020	19	0.47	9	2
Desulo	313	0.03	0.01	301	0.013	0.006	3	0.00	—	—
Galtellì	175	0.12	0.02	160	0.075	0.020	6	0.30	1	—
Lodè	163	0.29	0.03	180	0.125	0.024	22	0.45	10	1
S. Giusta	42	0.31	0.07	157	0.050	0.017	8	0.37	2	—
Siniscola	198	0.11	0.02	250	0.084	0.017	17	0.29	5	1
Terralba	100	0.30	0.05	282	0.075	0.015	not tested		not tested	
Teulada	101	0.17	0.04	242	0.070	0.016	13	0.15	2	3
Tonara	148	0.04	0.02	168	0.030	0.013	5	0.40	2	—
Total individuals	1,440			1,990			93	Total families	31	7

* The two estimates were obtained independently.

† This estimate was obtained by measuring the incidence of the enzyme deficiency among unrelated color-blind males.

‡ The classification of coupling and repulsion families was performed by examining the mothers and the male sibs of all color-blind propositi for G6PD activity.

that selection in favor of the gene for enzyme deficiency has been operative mainly in males, probably through a higher protection of the gene carriers against malaria. If, on the other hand, the gene for color blindness was slightly detrimental by itself but not sufficiently so to affect the fitness of its carriers when in coupling with the G6PD gene, this would explain the increase of the incidence of color blindness in areas in which the enzyme deficiency is common and would also account for the relatively higher incidence of enzyme deficiency among color-blind males as well as for the higher proportion of coupling phases in the general population. In other words, this would be an example of selection for a slightly detrimental gene owing to its close linkage with a highly adaptive one.

The second hypothesis, which does not actually exclude the previous one, takes into account the possibility of gene interactions between the protan, deutan, and G6PD loci. It could be assumed, for instance, that the X-chromosomal loci responsible for color vision and for G6PD activity are located in close vicinity in the sequence protan, deutan, G6PD. If these loci occupy a rather breakable part of the X chromosome, it is easy to imagine how deletions of different lengths could

give rise to defects in several of these genes. The deutan locus may be nearest to the locus for enzyme deficiency and a small deletion may involve both of these genes. A more extensive deletion may include the protan locus in addition.

Alternatively, we may think in modern terms[3] of these genes as parts of an operon. They might then be jointly controlled by a closely linked operator gene,

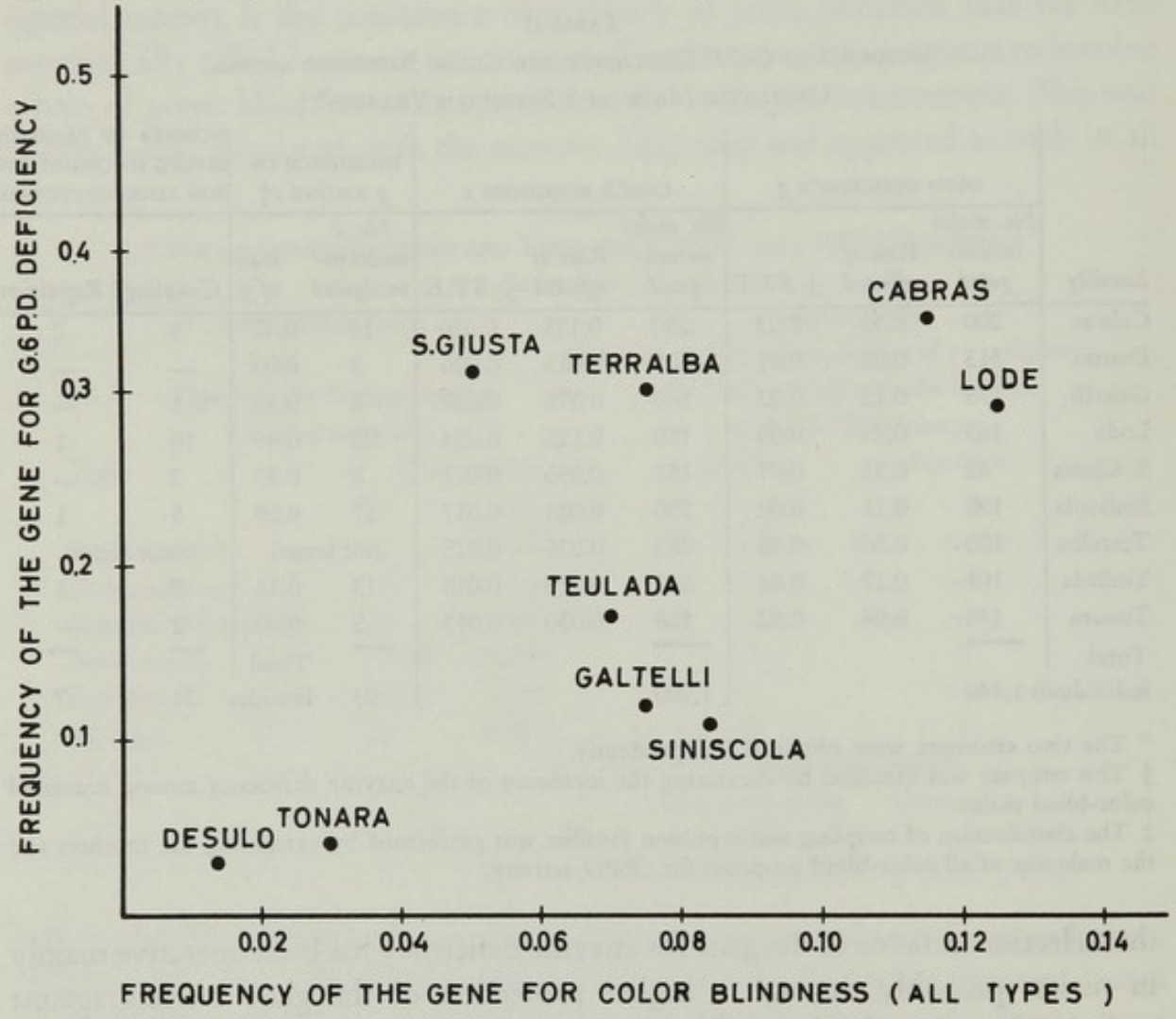


FIG. 24. Correlation between frequencies of color blindness and G6PD deficiency in Sardinian villages.

and multiple mutant phenotypes might result from mutational changes of this operator or of a more distant regulator.

On either model, such multiple defects, though probably quite detrimental in some environments, may have been maintained in Sardinia—thanks to the high adaptive value of the enzyme deficiency in the presence of malaria. These are, however, for the time being, only speculations and a great many more data are needed before firm conclusions may be drawn. Nevertheless, I mention this hypothesis mainly to invite other workers to collect critical data, which, in my opinion, should be looked for by checking the incidence of the enzyme deficiency

3 Jacob, F., and Monod, J., Genetic regulatory mechanisms in the synthesis of proteins, *J. Molecular Biol.*, *3*, 1961, 318-356.

among extreme deuteranopes in populations in which the G6PD gene is known to be very rare.

In conclusion, I should like to mention briefly the first results of our linkage studies with hemophilia, which are still in progress. Thus far we have been able to examine the families of 10 hemophiliac patients referred to us by Prof. Macciotta (Pediatric Clinic, University of Cagliari) and Prof. Breda (Medical Clinic, University of Sassari), and we have found only three families segregating also for the enzyme deficiency in an area where this trait is present in about 30 percent of the males. In each case the two defects are in repulsion, and this makes us feel that hemophilia plus enzyme deficiency may be a lethal association. One of these pedigrees apparently contains two recombinations, pointing toward a rather high recombination frequency. This is scanty information, but it indicates that it will be rather difficult to line up these 3 genes on the X chromosome unless more markers become available.

TABLE III

HYPOTHETICAL ADAPTIVE VALUES OF ENZYME-DFICIENT AND COLOR-BLIND MALES IN SARDINIA

Possible genotypes in males	*Genotype frequencies before selection*	*Fitness*	*Genotype frequencies after selection*
$g\ c^*$	pp'	1	pp'
$g\ +$	$p(1-p')$	1	$p(1-p')$
$+\ c$	$p'(1-p)$	$1-k'$	$p'(1-p)(1-k')$
$+\ +$	$(1-p)(1-p')$	$1-k$	$(1-p)(1-p')(1-k)$
	1	where $k' > k$	$1-(1-p)\,[\,p'(k'-k)+k\,]$

g = gene for G6PD deficiency.
c = gene for color blindness.

ALLISON: Mr. Adam is going to tell us very briefly about his linkage studies in Israel.

ADAM: Dr. Siniscalco has already emphasized the difference between his results and ours. Table I shows our segregation data for 19 Jewish families. As can be seen, in 16 families the mutant genes were in repulsion and only 3 sibships showed coupling. The families belong to the communities of Baghdad and Kurdistan.

These families were ascertained by either of two methods. Families of color-blind males were investigated for the enzymatic defect, and families of G6PD-deficient males were tested for color vision.

The excess of repulsion between the mutant genes observed in these families cannot be due to the mode of ascertainment. We were able, indeed, to show by a different approach that the distribution of the two defects in the Iraqi community is not random. We tested 65 unrelated color-blind Iraqi Jews for G6PD activity. Since the frequency of G6PD deficiency in this community is 25 percent, about 15 of these 65 are expected to suffer also from enzyme deficiency, but actually we found only 8. We may thus conclude that chromosomes with only one of the

defects are more common in this community than expected in a population at equilibrium.

Dr. Siniscalco assumes that the equilibrium may be disturbed by viability differentials. This line of thought enforces the additional assumption that the association of the two mutant genes was advantageous in Sardinia but deleterious in the Jews of Baghdad. I should like to suggest another explanation for the repulsion of the two defects in the Iraqi community. This congregation has an ancient tradition and is known to have been established in Mesopotamia for over 2000 years. There are, however, historical records of two severe epidemics—

TABLE I

SEGREGATION OF COLOR BLINDNESS AND G6PD DEFICIENCY AMONG MALE SIBLINGS IN 19 FAMILIES

COLOR VISION:	DEFICIENT		NORMAL		*No.*	*No.*
enzyme activity:	*deficient*	*normal*	*deficient*	*normal*	*families*	*males*
Phenotypes	—	31	25	—	16	56
Phenotypes	11	—	—	8	3	19

cholera and plague—which afflicted Iraq and especially Baghdad during the eighteenth century and decimated both the Jewish and Moslem populations. Another epidemic, coinciding with a flood of the Tigris River in 1831, wiped out a large proportion of the population. Many of the surviving Jews emigrated to other countries and some of these founded new Jewish communities in India and the Far East. The recovery of the city of Baghdad and its Jewish community began only about a hundred years ago, especially after the construction of the Suez Canal; at the time of this recovery, many Jewish immigrants from other countries joined this community, mainly from Iran but also from Kurdistan and from several other countries of the Turkish Empire. The majority of these communities are known to have lower frequencies of enzyme deficiency than the present-day Iraqi Jews. Therefore, the genes for color blindness introduced into this community a few generations ago were borne on X chromosomes free of the enzyme deficiency.

It will be only a matter of time before a new equilibrium is brought about between the repulsion and the coupling phases of the two genes by recurrent crossing over. Since we found no cases of recombination among our families, it is clear that the two loci are very closely linked. It is supposed, therefore, that the time elapsed since the above-mentioned migrations was too short to establish equilibrium.

ALLISON: I think this does pose an interesting problem and raises the possibility of the independent origin of these mutant genes. The other possibilities will be considered by Dr. Morton.

MORTON: We have heard during the course of this meeting a number of references to what must certainly be drift. I think there is no reasonable doubt that drift explains the excess of coupling between primaquine sensitivity and color

blindness in one population and of repulsion in another. Consider the very close linkage between these genes and the unlikelihood of their interaction. When primaquine sensitivity was introduced into this population either by mutation or by one or two migrants, there was at that time and for several generations thereafter a bottleneck. The trait was present in a few individuals who had a higher frequency of color blindness than the population average or a lower one. Under these conditions it would take a very long time before equilibrium could be reached.

ALLISON: I want to say just a few words about the question of selection operating on sex-linked loci. Now, as everyone knows, for two alleles at an autosomal locus an advantage of the heterozygote will give rise to a stable equilibrium. Whatever the fitness of the homozygotes, an equilibrium level will be reached and both allelic genes will be maintained in the population. The same will happen at a sex-linked locus if there is an advantage of the female heterozygote. However, there has been some argument about whether an equilibrium can be established when there is only an advantage of the male hemizygote. If this is possible at all, it appears to happen under a very limited range of conditions. Hence, the selection with which we are concerned is really that which operates on the female heterozygotes.

In this connection we should recall that the manifestation of sex-linked genes poses yet another problem. According to the argument developed particularly by Dr. Mary Lyon,[1] only one of a pair of X-linked genes may be active in the cells of female heterozygotes. She has shown—and others have produced similar evidence—that one of the X chromosomes is heteropycnotic in virtually all of the cells of all females, and it is this heteropycnosis that gives rise to the well-known sex chromatin. As a result of this, in clones of cells in heterozygotes either the normal or the abnormal gene will be active. There is a lot of evidence that this happens in animals. Several sex-linked genes giving mottled or dappled coat color in female mice are known—for example, "tabby." It is true also of the tortoiseshell cat. In clones of cells in heterozygous females one finds either the full operation of the normal gene or one finds the deficient gene fully manifested, as it is over the whole body of mutant males.

Typical sex chromatin occurs in man. Thus, in G6PD deficiency we would expect to find clones of cells in female heterozygotes, some with high and others with low enzyme activity, and this is a point that I think deserves investigation. It has a direct bearing, of course, on susceptibility to hemolysis, growth of malaria parasites, and hence the problem of selection operating on these genes. The proportion of cells manifesting these two characteristics will vary in different heterozygotes. This may give rise to a wide variation of enzyme activity in heterozygotes, as indeed is observed, most being intermediate but some resembling the abnormal hemizygotes and others resembling the normal homozygotes.

1 Lyon, M. F., Sex chromatin and gene action in the Mammalian X chromosome, *Am. J. Human Gen.*, *14*, 1962, 135-148.

Now, finally, I should like to call on Prof. Adler, who has great experience with variation in malaria parasites. It is conceivable that malaria parasites could become adapted to multiply more favorably in the red cells of subjects possessing the sickle-cell trait or enzyme deficiency in areas where these genes are common, thus providing a nice example of secondary adaptation to an altered host. Prof. Adler will consider this possibility.

S. ADLER

Remarks on the Host Range of Some Malaria Parasites

Many points of interest to malariologists have arisen in this discussion, one of them being the problem of sickling. Apparently sickling, which is a deleterious trait, is less so than an infection with *Plasmodium falciparum* and therefore it is claimed that in endemic foci of malignant tertian malaria natural selection has favored sicklers against nonsicklers.

Attempts have been made to investigate this point experimentally but, though impressive, the results are not absolutely conclusive. The problem may be attacked by *in vitro* experiments. It is not easy to maintain many generations of human malaria parasites *in vitro,* but it is relatively easy to keep a few generations. I would suggest that cultures of malaria be made on sickling blood and compared to cultures on normal blood. This should give some interesting information.

The sickling trait is not the only genetic factor associated with protection against malaria. We have the remarkable fact that enormous sections, if not all, of the native population of West Africa are immune to *Plasmodium vivax,* the commonest of all malaria parasites outside West Africa. It is readily transmitted by mosquitoes and plays havoc with populations in endemic foci. This parasite is virtually absent from large areas of West Africa, although conditions for transmission are ideal.

Recently Dr. Bray[1] has carried out an experiment in Liberia in which he attempted to inoculate thirty indigenous West African volunteers with *Plasmodium vivax*. The results were interesting. He did get a slight infection in one case but nothing to compare with infections of *Plasmodium vivax* as they occur outside West Africa. The others were negative.

Interestingly enough, this population, which is immune to *Plasmodium vivax,* is very susceptible to *Plasmodium ovale,* a malaria parasite which is rare outside

1 Bray, R. S., The susceptibility of Liberians to the Madagascar strain of *Plasmodium vivax, J. Parasitol., 44,* 1958, 371-373.

Africa; either the majority of the human species has a natural resistance, or the parasite cannot compete with *Plasmodium vivax* in a population susceptible to both. This is also a point which remains to be investigated experimentally. Nearly all the malarias reported in the past from West Africa as *Plasmodium vivax* were almost certainly *Plasmodium ovale;* the criteria for a correct diagnosis have been established only within recent years.[2]

I would like also to say a few words about hemolysis in malaria. It has been proved beyond doubt that G6PD deficiency in red cells is one potential factor in hemolysis, but it should be realized that hemolysis may be an extremely complicated phenomenon. The red cell is a fantastically complex piece of chemical machinery, and many factors may be involved in hemolysis. A deficiency of the dehydrogenase should not be invoked to explain all cases of hemolysis.

It is a very striking fact that 40 to 50 years ago there were a large number of cases of blackwater fever in this country and that they occurred mainly among Ashkenazim of European origin—that is to say, in people who are apparently free of this dehydrogenase deficiency. We have the same experience in West Africa. Most of the deaths from blackwater fever in West Africa, and in England in people returning from West Africa, occurred in Europeans—*i.e.*, again individuals who probably did not have this dehydrogenase deficiency. There are many factors in hemolysis, and no single explanation should be offered for all cases.

I would like to speak briefly, at Dr. Allison's request, on the question of adaptation of malaria parasites to various hosts. Consider two malaria parasites of rodents—namely, *Plasmodium berghei* and *Plasmodium vinckei:* the former prefers young cells whereas *Plasmodium vinckei* prefers mature cells and, in the presence of both mature and young cells, the latter parasite will usually infest the mature cells. Nevertheless, when the bulk of the red-cell population consists of reticulocytes (a condition easily produced in mice), *Plasmodium vinckei* readily invades them.[3] It quickly adapts itself to the prevalent type of red cell in the mouse.

Let us consider the case of the malaria parasites of man and those of anthropoid apes. Morphologically they are quite indistinguishable. You cannot infect a normal nonsplenectomized chimpanzee with *Plasmodium falciparum* from man; neither can you produce an appreciable infection of *Plasmodium vivax* by inoculating it with infected human blood. Vice versa, the inoculation of a human being with a chimpanzee parasite which looks exactly like *Plasmodium falciparum* gives a negative result and this also applies to *Plasmodium vivax var. Schwetzi,* a parasite of the chimpanzee which resembles *Plasmodium vivax.* On the other hand, *Plasmodium malariae* (the parasite causing quartian malaria) is readily transmitted from the chimpanzee to man. Now, these parasites of the chimpanzee and man are so similar that they must have a common origin. Nevertheless, they have become

2 Garnham, P. C. C., Bray, R. S., Cooper, W., Lainson, R., Awad, F. I., and Williamson, J., The pre-erythrocytic stage of *Plasmodium ovale, Trans. Roy. Soc. Trop. Med. Hyg., 49,* 1955, 158-167.

3 Adler, S., and Foner, A., Observations on *Plasmodium vinckei* before and after adaptation to splenectomised hamsters, *Bull. Res. Council Israel, 9E,* 1961, 1-23.

specialized and have narrowed what one may call their spectrum of infectivity, probably as a result of restriction by ecological factors to a single host. It is interesting to note that a splenectomized chimpanzee can be infected with *Plasmodium vivax*, as Prof. Garnham and his colleagues[4] have shown. Under natural conditions the above-mentioned two chimpanzee parasites will not infect man, and the two human parasites will not infect the chimpanzee. Restriction to a single host over long periods may be one of the factors in the speciation of some malaria parasites. It is therefore surprising that a malaria parasite of a cynomolgus monkey, *Plasmodium cynomolgi bastianellii*, which one would expect to be much more alien to humans than chimpanzee malaria parasites, is easily transmissible to man both by direct inoculation and by mosquitoes. It is quite impossible to predict *a priori* how a malaria parasite will adapt itself to different hosts. Obviously, the capacity to adapt must depend on several innate and hitherto unknown genetic factors present in either parasite or host.

My colleagues, Dr. A. Foner and Dr. A. Gunders, and I tried a model experiment on adaptation with a rodent malaria parasite, *Plasmodium vinckei*. This appeared to be promising material for experiments on adaptation which have now continued for six years.[5] Originally *Plasmodium vinckei* did not produce appreciable infections in hamsters. It was therefore interesting to see whether it could be adapted to the hamster. Eventually it became adapted to splenectomized hamsters. Its behavior in splenectomized hamsters remained constant for more than three years, during which period it produced fairly heavy infections and a mortality of about 10 percent. Recently it has become adapted to normal hamsters, in which it now produces considerable infections.

The original strain produced a 100-percent mortality in the mouse. After it had been adapted to the hamster, it became less pathogenic for the mouse, in which it still produced heavy infections and a severe anemia but a mortality of only 20 percent. Restriction to a single host over a long period had changed something, but this change was not permanent. After a number of passages (12 to 13) of the hamster-adapted strain in mice the mortality of the latter returned to 100 percent, but infectivity for hamsters was fully maintained. These results could not have been predicted. In some hosts we get a rapid adaptation of a particular parasite; in others no adaptation occurs.

The malaria parasites of man have apparently remained constant over a long period (except for strains which develop permanent resistance to specific drugs). Apart from West Africans, who are immune to *Plasmodium vivax*, nearly the entire human race is susceptible to these parasites. The whole subject is full of

4 Garnham, P. C. C., Lainson, R., and Gunders, A. E., Some observations on malaria parasites in a chimpanzee, with particular reference to the persistence of *Plasmodium reichenowi* and *Plasmodium vivax*, *Ann. Soc. belge Med. trop.*, *36*, 1956, 811.

5 Adler, S., and Foner, A., *loc. cit.*

possibilities for experimental work of interest both to the malariologist and to the geneticist.

ALLISON: Thank you very much, Prof. Adler, for this interesting account. It is clear that we really do not know what to expect in the human situation, but I think it is at least encouraging that these blood parasites show such remarkable selectivity in terms of their species specificity. This suggests that minor variations in red cells may be enough to afford protection. It is conceivable that parasite strains could arise which would be adapted to the erythrocyte defects. But for reasons which I will not go into now, it may be supposed that such strains would not spread in the populations concerned.

Our president would like to add some remarks.

HALDANE: First, I should like to make one comment on these hemoglobin studies. It is striking that, although the main function of hemoglobin appears to be to carry around oxygen, no studies appear to have been made on the function of the abnormal hemoglobin from that point of view. There is no doubt that their total oxygen capacity will be the same. But there are many other important parameters—the static parameters, such as the amount of oxygen needed to half saturate them in various circumstances, and dynamic parameters, such as the rate at which they give up oxygen under given circumstances of temperature, for instance.

Now, most of those parameters vary to a considerable extent with the concentration of hemoglobin, the concentration of salts or of hydrogen ions, and so on. There appears to be one which is very largely independent of those and a function of the hemoglobin itself—at any rate, at a given temperature—and this is the relative affinity of the hemoglobin for oxygen and carbon monoxide. This undoubtedly varies among animal species. I have some doubt as to whether it varies among human beings. It seems to me that it would be very easy in a few weeks' work to determine whether that character varies, as, of course, the solubility of the hemoglobins varies and the mobilities of the various hemoglobins vary, but I get the strong feeling that we have been looking at, what shall I say, rather artificial, rather unphysiological characters of these abnormal hemoglobins. It might be worth considering some of their physiologically important characters.

The second point I want to make is this: like Dr. Allison, I thought of Lyon's hypothesis as to the action of sex-linked genes in heterozygous females. On this hypothesis they act in some cells and not in others. And I thought how interesting it would be if we could get some means of determining whether an individual cell was enzyme-deficient or not, and then Dr. Sheba showed us these beautiful photographs (see Figs. 20 and 21) which enable him to determine just that. It seems to me that it will be of very great interest to look at a number of heterozygous females to see whether in each of them there is a sharp division between normal

cells and deficient cells and, if so, in what concentration, in what proportions these types occur. Dr. Sheba tells me that he already has some data of this kind. I can only say that if he will follow up that work, whatever the value may be for medicine, it will be of very great value for genetics as showing that this difference which one sees in the phenotype, on tortoise-shell cats, on tabby mice, and so on, actually occurs at the cellular level.

A third point is that I cannot agree with Dr. Allison that in order to stabilize polymorphism either at a sex-linked or at an autosomal locus it is necessary that the heterozygotes should be fitter. In each case, it is quite possible to obtain a stable polymorphism if selection is in different directions in the two sexes. I do not say that that is a likely event. But if perhaps in some case the fertility of females is an important selective factor and in others it is not, it is at least possible that a polymorphism may be stabilized in that way.

ALLISON: Thank you, Prof. Haldane. And this brings us to the end of the morning's session. I think you will agree that we have had an interesting time, and that, although we have a lot of information on these points, there is a very great deal that still needs to be done.

SESSION 3 A. G. STEINBERG, *Chairman*

THE INFLUENCE OF ENVIRONMENTAL CHANGES AND ETHNIC FACTORS ON THE INCIDENCE OF SOME COMMON DISEASES AND MALFORMATIONS

STEINBERG: This session is to be centered around the influence of environmental changes and ethnic factors on the incidence of some common diseases and malformations. In many respects it may be considered as a continuation of the previous session, in which we discussed the frequencies of various erythrocyte defects and their dependence on environmental conditions.

I should perhaps point out that almost throughout the previous debate environment was regarded merely as the total of selective forces favoring one or the other genotype. When we come to consider atherosclerosis or diabetes, environment will assume a more complex role.

We must keep in mind that a given genotype may develop into widely differing phenotypes under the influence of various environments. Environmental agencies act in the first place by molding the phenotype, inhibiting or promoting the penetrance and the expressivity of an inherited condition. The phenotype so produced will continue to be exposed to environmental forces, which now exert a discriminating or selective function.

Dr. Ungar will analyze this complicated nature-nurture interaction with reference to atherosclerosis and myocardial infarction in various Jewish groups in Israel.

H. UNGAR, A. LAUFER, Z. BEN-ISHAY

Atherosclerosis and Myocardial Infarction in Various Jewish Groups in Israel*

About twelve years ago, clinicians and statisticians in Israel pointed out that myocardial infarctions are about three times as frequent in the Ashkenazic group of the Jewish population in Israel as in immigrants from Asia and North Africa.[1,2] These first reports were followed by laboratory studies revealing significantly higher levels of blood lipids in the population of "Western" origin as compared with those from the East.[3] The observations suggested that the low values of blood lipids were characteristic of the *new* immigrants from the East whereas the blood-lipid level appeared to rise with prolonged stay in the new country.[4]

* Supported by Grants H-3942 and H-3942 (C-1) from the National Heart Institute, U.S. Public Health Service.

1 Dreyfuss, F., The incidence of myocardial infarctions in various communities in Israel, *Am. Heart J., 45,* 1953, 749-755.

2 Dreyfuss, F., Toor, M., Agmon, J., and Zlotnik, A., Observations on myocardial infarctions in Israel, *Cardiologia, 6,* 1957, 387-398.

3 Brunner, D., and Loebl, K., Serum cholesterol, electrophoretic pattern, diet and coronary artery disease: a study in coronary patients and in healthy men of different origin and occupations in Israel, *Ann. Int. Med., 49,* 1958, 732-750.

4 Toor, M., Katchalsky, A., Agmon, J., and Allalouf, D., Atherosclerosis and related factors in immigrants to Israel, *Circulation, 22,* 1960, 265-279.

Mortality statistics for the entire population of Israel have confirmed the clinical impression of a higher prevalence of myocardial infarction in Ashkenazic Jews.[5] However, within the "Eastern" group, no difference in mortality has been found between new immigrants and old settlers, although this might have been expected on the basis of the laboratory studies of blood lipids.

In view of these findings we have begun a survey on the incidence and degree of atherosclerosis in a continuous series of autopsies. A preliminary report of the results has been published[6] (see also p. 318). The present communication is concerned with a larger series of 842 consecutive autopsies observed over a period of two years in males and females 30 years of age and older.

The validity of autopsies in epidemiological surveys has often been questioned. A post-mortem sample will never be a random sample until it will be possible to ensure that every death occurring in a given population will be brought to autopsy. The variety of factors involved in producing the bias of autopsy surveys was analyzed not long ago by a study group and will be summarized briefly.[7] The composition of autopsy samples may depend to a large extent on the admission policy of hospitals. Certain hospitals are inclined to admit more acute patients; others admit mainly the aged and chronically ill. The interest of the hospital staff or the requirements of teaching also have a bearing on the selection. Social factors also come into play. In some communities fewer women elect to be admitted for treatment, because of religious or economic reasons. Finally, the issuance of autopsy permits is dependent on religious and sometimes political considerations. In spite of the bias with which an autopsy sample is usually loaded, it is of advantage to study a continuous series of autopsies for various pathological features. Regarding atherosclerosis, many cases of varying degree may be discovered in the general hospital population which were only of incidental interest or unknown to the clinician during the terminal disease of the patient.

For the appraisal of atherosclerosis in the aorta and in the coronaries, a standardized and internationally accepted method was used.[8] For the aorta, we have used a formula proposed by Gore and Tejada[9] which takes into consideration the extent of the lesion and the percentage of the surface involved and gives a certain weighting to the various degrees of anatomical lesions, starting with the lipid streaks and ending with complex lesions involving calcification and thrombosis (Fig. 25).

Regarding the coronaries, no ideal solution has been found thus far. Again we have employed the formula suggested by Gore and Tejada,[10] which stresses the

5 Kallner, G., Epidemiology of arteriosclerosis in Israel, *Lancet, 1,* 1958, 1155-1156.

6 Ungar, H., and Laufer, A., Necropsy survey of atherosclerosis in the Jewish population of Israel, *Path. Microbiol., 24,* 1961, 711-717.

7 Doll, R. (Ed.), *Methods of Geographic Pathology. Report of a Study Group Convened by the C.I.O.M.S.,* Blackwell, Oxford, 1959.

8 *Classification of Atherosclerotic Lesion. Report of a Study Group,* World Health Organization Technical Report Series 143, 1958.

9 Gore, I., and Tejada, C., The quantitative appraisal of atherosclerosis, *Am. J. Path., 33,* 1957, 875-885.

10 *Ibid.*

physiological effect of atherosclerosis rather than the anatomic lesion. The index determined by this empiric formula relies on the extent of luminal narrowing of more than 50 percent in the course of the coronary system. In view of the fact that the right and left coronary arteries are joined by collaterals which in the young patient are only of anatomic importance but may become functional with progressing atherosclerosis, we follow Gore and Tejada[11] in considering the entire coronary system as one hypothetical vessel.

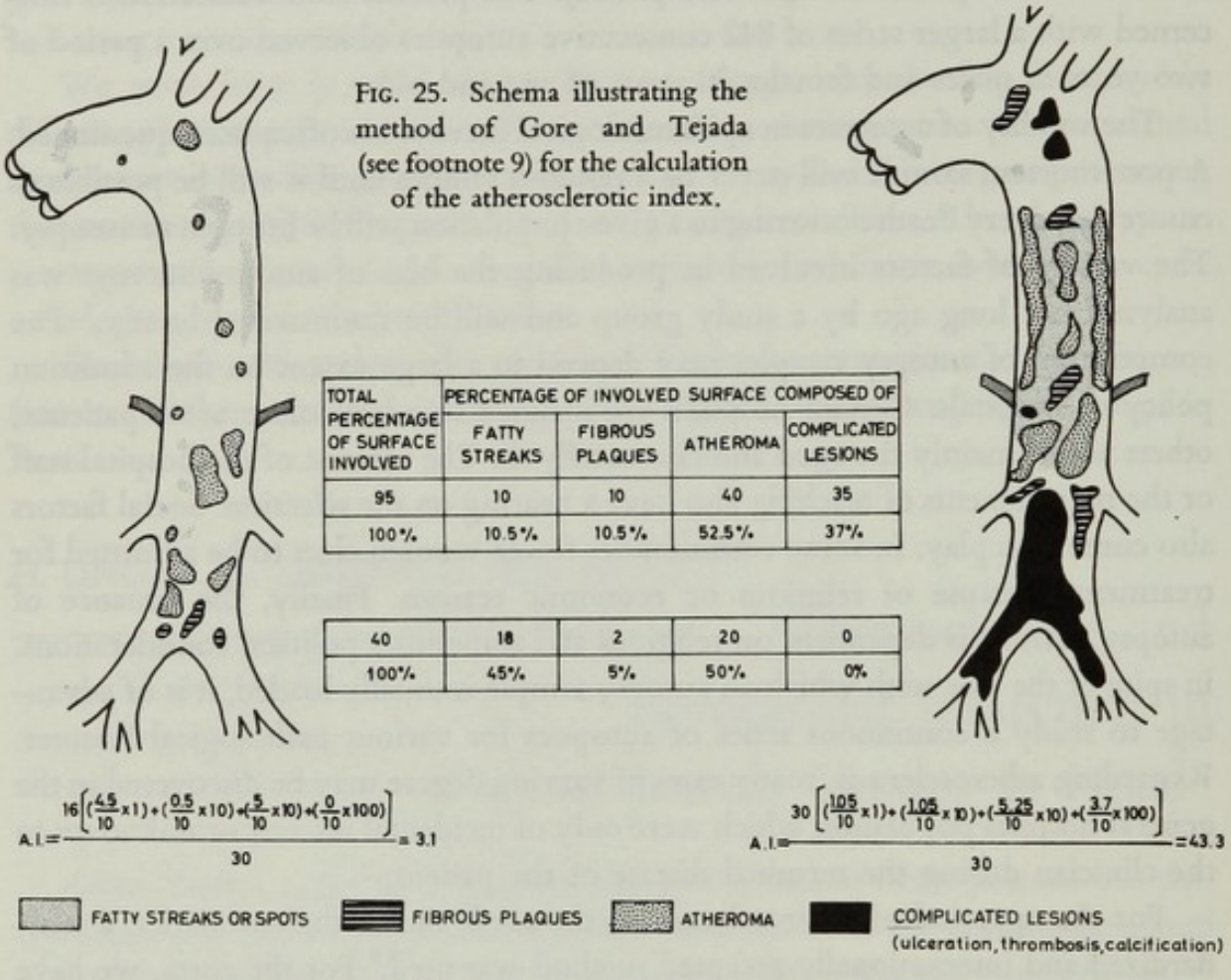


FIG. 25. Schema illustrating the method of Gore and Tejada (see footnote 9) for the calculation of the atherosclerotic index.

Our sample consisted of members of the various Jewish communities of Israel. Since several communities were represented in very small numbers (see also p. 318) we have arranged the material for the time being in two major groups—Ashkenazim ($N = 568$) and non-Ashkenazim ($N = 274$).

RESULTS

Among the 568 autopsies of Ashkenazim we encountered about 20 percent of cases of acute myocardial infarction, whereas in the series of non-Ashkenazim there were only about 8 percent of such cases (Table I).

If we subdivide our series into two age groups, the difference between acute myocardial infarction in the non-Ashkenazic and the Ashkenazic group becomes

11 *Ibid.*

more prominent (Fig. 26). There was not a single case of acute myocardial infarction as cause of death in the non-Ashkenazic group before the age of 50, whereas among Ashkenazim there were 10 percent of such cases.

These findings appear to confirm the clinical reports. However, the distribution of myocardial scars, resulting from clinically unrecorded ischemic events, presents a more complex picture. For this part of our investigation, we have excluded from the entire series 52 cases exhibiting scattered fibrous patches of less than 10-mm. diameter in the myocardium. Such lesions are considered by some authors as evidence of preceding minute infarctions,[12] but at present we are unable to deny the possibility that they may be the result of gradual replacement during chronic ischemia or represent remnants of inflammation.

TABLE I

CASES OF ACUTE MYOCARDIAL INFARCTION BY AGE, SEX, AND COMMUNITY

	ASHKENAZIM		NON-ASHKENAZIM		TOTAL	
Age	*M*	*F*	*M*	*F*	*M*	*F*
30-39	—	1 (—)*	—	—	—	1 (—)
40-49	10 (4)	3 (1)	—	—	10 (4)	3 (1)
50-59	22 (4)	7 (4)	7 (3)	—	29 (7)	7 (4)
60-69	33 (9)	9 (2)	6 (2)	3 (2)	39 (11)	12 (4)
70+	16 (3)	14 (5)	4 (2)	2 (1)	20 (5)	16 (6)
Total	81 (20)	34 (12)	17 (7)	5 (3)	98 (27)	39 (15)
No. of cases examined and % of Ac. My. Infarction	568—20.2%		274—8.03%		842—16.3%	

* Numbers in parentheses indicate cases in which the first infarction was fatal; of the other cases, 88 had signs of previous ischemic episodes with scars and 7 with scattered fibrous patches.

Among the remaining 790 cases no scars have occurred in the non-Ashkenazic group below the age of 50. In the older age group, the incidence of scars was 17 and 14 percent respectively in the two population sectors, a difference of no statistical significance (Fig. 26).

The relationship of findings in the myocardium to the lesions in the aorta and the coronaries has been investigated. The series of 790 autopsies has been divided into cases presenting ischemic myocardial lesions, acute or healed, and cases without gross lesions in the myocardium. For each of the two groups the atherosclerotic indices are presented in Figure 27 and the mean narrowing indices of the coronaries in Figure 28. No sex difference was observed in any age group or ethnic sector and therefore the data for both sexes have been combined in Figures 27 and 28. In both diagrams, for every decade, the first two bars on the left present the means and standard errors of the atherosclerotic indices for cases with myocardial lesions and the two bars on the right present the same values for cases having an intact myo-

12 Edwards, J. E., Correlations in coronary arterial disease, *Bull. N. Y. Acad. Med., 33*, 1959, 199-217.

cardium. It was found that atherosclerosis in the aorta was considerably more severe in the group with ischemic heart disease (Fig. 27). Comparison among communities was not possible in the fourth and fifth decade for cases with myocardial lesions in view of the absence of such cases in the non-Ashkenazic group. However, no ethnic differences were found in any other group.

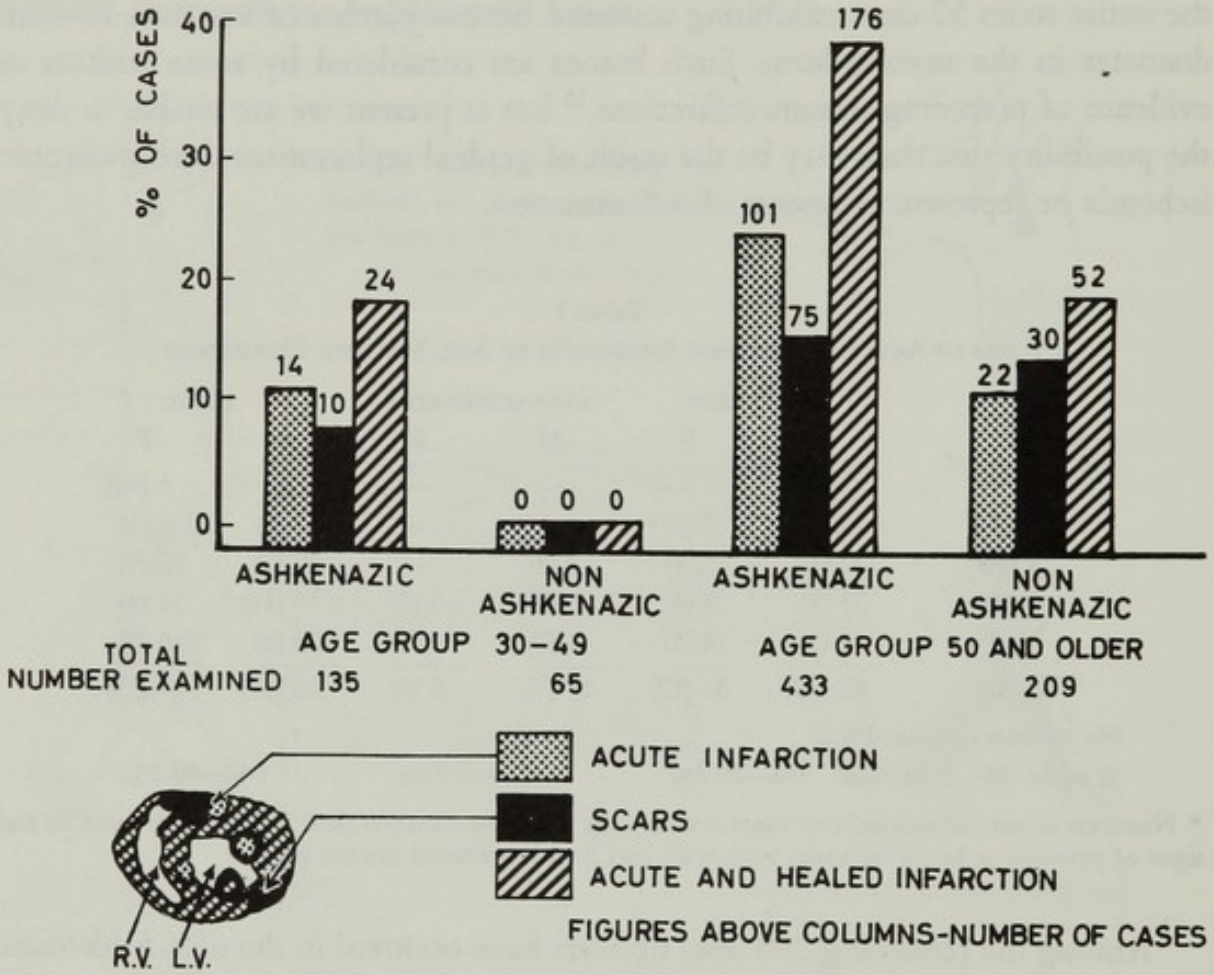


FIG. 26. Rate of affection at autopsy with myocardial infarction and scars in Ashkenazim and non-Ashkenazim of two age groups.

The means of the narrowing indices of the coronary arteries (Fig. 28) in the group with ischemic lesions were significantly higher than in the control group. Again no ethnic differences were observed in the cases free of myocardial damage. However, in the cases showing acute or healed myocardial lesions, the narrowing indices in the Ashkenazic group of the sixth and seventh decades were significantly higher than in the non-Ashkenazim of corresponding ages. On the other hand, the mean indices in this latter group signify three points of narrowing and thus are well within the range where ischemic lesions might easily be expected.

COMMENT

The present series is still too small to permit further subdivision according to duration of stay in Israel, although the need for such a study is suggested by clinical

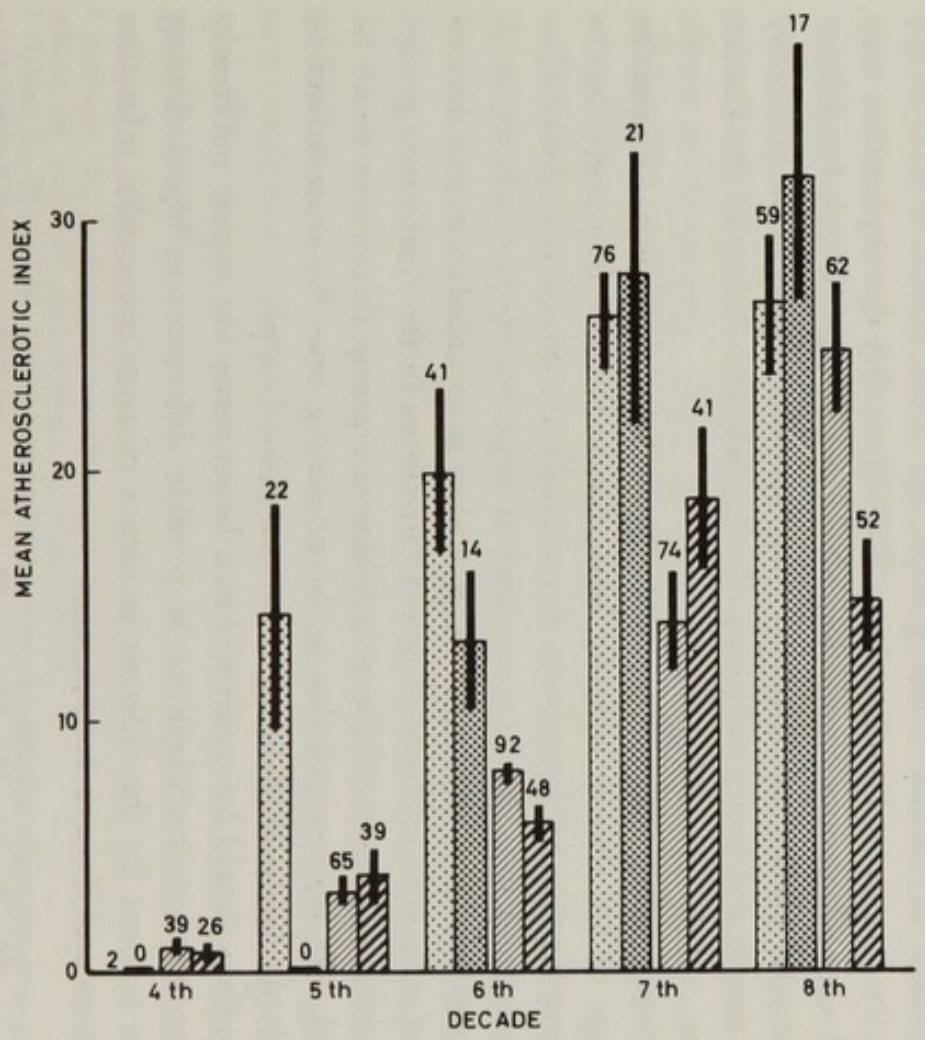
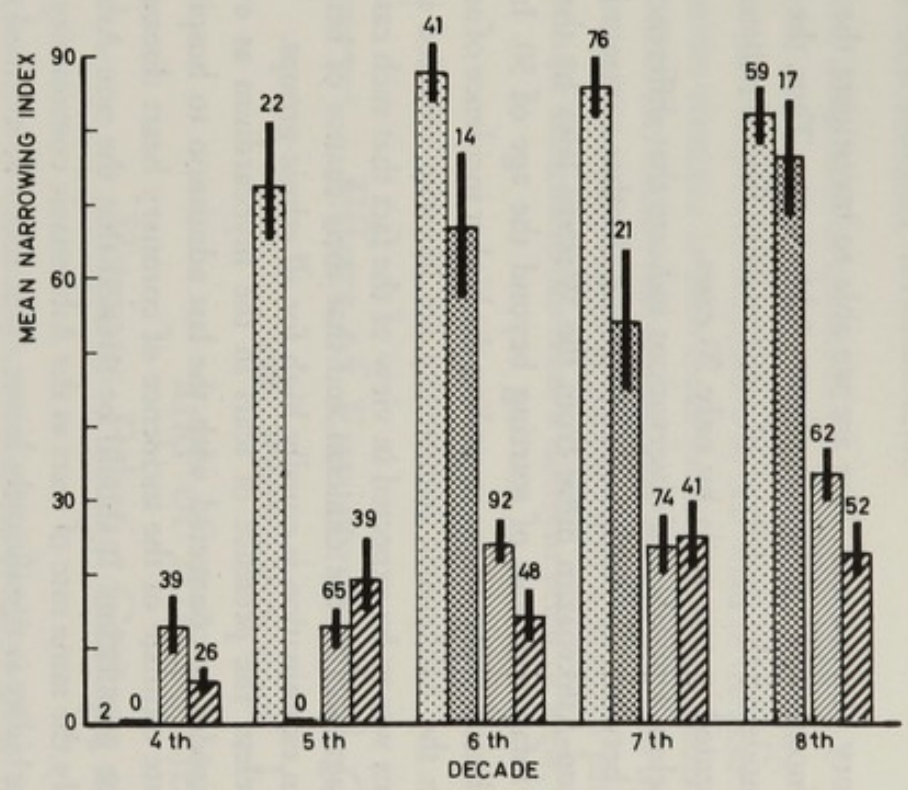


FIG. 27. Mean atherosclerotic index (aorta) in autopsy cases with and without myocardial lesions classed by population sector and decade of life. Black bars indicate extent of ± 1 ST.E.



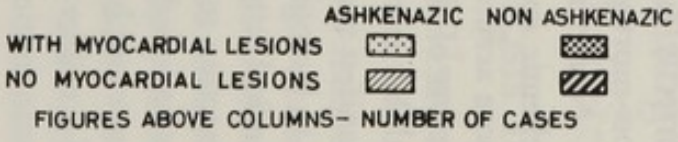


FIG. 28. Mean narrowing index (coronaries) in autopsy cases with and without myocardial lesions classed by population sector and decade of life. Black bars indicate extent of ± 1 ST. E.

and laboratory observations. Nor are we able to investigate the differences that may exist among the communities of non-Ashkenazim. Thus, the Yemenite Jews, who are considered the prototype of a community free of ischemic heart disease, were represented in our series by only 20 cases.

Nevertheless, a number of observations indicate that differences in morbidity exist indeed between the Ashkenazic group and all other communities. In the first place, the non-Ashkenazim differ from the Western Jews by the delay of acute myocardial infarctions and of scarring beyond the age of 50. In the older age group, the clinical observations regarding the higher incidence of acute myocardial infarction in the Ashkenazic community are likewise reflected in post-mortem findings. This was to be expected in view of the fact that such cases are, as a rule, correctly diagnosed by the clinician and that their chance of being subjected to post-mortem examination is equally high for all ethnic groups.

Nevertheless, the presence of scars in the myocardium as evidence of past ischemic episodes, unconnected with the last admission to hospital, may give a more accurate estimate of the incidence of coronary heart disease in the various sectors of the population. It should be stressed that the non-Ashkenazic groups exhibit nearly the same rate of scars as the Ashkenazic community, although their manifest morbidity is significantly lower. This could be ascribed to social as well as to biological factors. Thus it could be assumed that because of different levels of medical attention in various ethnic groups, the acute disease would escape detection in the less favored communities. We believe that this explanation may be excluded since the various communities have similar rates of Sick-Fund Insurance and hospital admissions. Attention must therefore be paid to the possibility of a milder course and better prognosis of atherosclerotic disease in the Eastern communities.

In a previous communication[13] we have suggested that, in the non-Ashkenazim above the age of 50, chronic ischemic heart disease is more frequently due to gradual narrowing than to thrombosis. Accordingly, the disease would take a less dramatic course and thus not be recognized as requiring hospital admission. A search for coronary thrombosis in our series of acute myocardial infarction showed 77 percent of cases with evidence of recent thrombosis in the Ashkenazic group, whereas in only 46 percent of the non-Ashkenazic group thrombosis could be demonstrated. We may assume that in the remaining cases the acute infarction was the result of relative insufficiency of coronary blood supply.

These findings should be confirmed in a larger series but appear sufficiently interesting to warrant investigations of possible differences in blood clotting properties to account for the different incidence of acute myocardial infarction in the Western and Eastern communities.

STEINBERG: Thank you, Dr. Ungar. You have made it very plausible that,

13 Ungar, H., and Laufer, A., *loc. cit.*

discounting all the differences in modes of life among the various ethnic groups, there may still be a residue of genuine genetic variance among them. You should be able to obtain the complete confirmation of this point in the near future if the various communities continue in their rapid process of "westernization."

I wonder whether Dr. Cohen will support you. He will first deal with diabetes, another morbid condition believed to be promoted by a Western pattern of life, and will then consider atherosclerosis from a different point of view.

A. M. COHEN

Effect of Environmental Changes on Prevalence of Diabetes and of Atherosclerosis in Various Ethnic Groups in Israel

Diabetes is considered to be based on an inherited predisposition. It is accepted in the literature that the Jewish people are especially disposed toward this disease, although no definite proof or figures are given. The clinical experience of physicians in this country, of Steinitz,[1] Gutmann,[2] Nelken,[3] and ourselves, did not agree with this concept. In 1954 I visited Joslin and pointed out our disagreement. He did not appear convinced and he asked me: "Did you examine the population?" So I returned and began to examine the population.[4] The method of study was a field survey in closed areas. These included several quarters of Jerusalem and about twenty-four settlements in the Jerusalem corridor, in the Lydda District and around Beersheba.

For reasons you have already heard about, the Yemenites were classified separately from the other non-Ashkenazim and so were the Jews from Kurdistan and Cochin. Of the non-Ashkenazic Jews we examined about 4150 persons; of the Ashkenazim about 4300. The Yemenites were divided into two groups: (1) about 5000 newcomers to this country who had arrived during the past ten years and (2) 751 old settled Yemenites from Jerusalem. Similarly, we distinguished between new immigrants from Kurdistan (about 1000) and old settlers originating in that area (about 500). In all we examined about 15,000 persons. About 90 percent of the population in the areas were included in the study. The others were not included

1 Steinitz, H., The incidence of diabetes in Israel, *Harefuah, 50,* 1956, 106.

2 Gutmann, M. J., Antagonism between diabetes mellitus and allergic diseases especially bronchial asthma, *Int. Arch. All. Appl. Immunol., 4,* 1953, 118-128.

3 Nelken, L., The incidence of diabetes mellitus among the different ethnic groups in Jerusalem (Hebrew), *Dapim Refuiim, 14,* 1955, 293.

4 Cohen, A. M., Prevalence of diabetes among different ethnic Jewish groups in Israel, *Metabolism, 10,* 1961, 50-58.

for reasons of hospitalization or service in the army or for some other reasons, including lack of cooperation.

Now, in order to determine whether the age distribution of our sample was representative of the population, we compared it with the official government statistics for 1957.[5] (Our study was done during the year 1958-1959.) We subdivided the studied population into age groups of 20-39, 40-49, and so on. In the official statistics we could not get figures below the age of 20 years for comparison, because the government regards every child born in this country as "Israeli," whereas we group individuals according to the country of origin of the father or the grandfathers. Our Ashkenazic sample contained a higher representation of persons aged 20-39 than expected according to the government data. This again may be due to the official classification of some of these persons as "Israelis." But on the whole the age distribution of our sample (see figure on p. 325) was in good agreement with that of the general population. The fit was even better in the non-Ashkenazic group, probably because fewer persons of these communities are born in Israel.

We wanted to see whether our survey could be compared directly with similar studies abroad. It turned out that the age distribution of our sample agrees very well with that of Wilkerson and Krall's survey[6] in Oxford (see figure on p. 325). We are therefore entitled to compare the over-all diabetes incidence disclosed by our survey with the results of similar surveys in the United States and probably with the incidence in other Western countries.

Our study was based mainly on examination of postprandial urine, collected after the preliminary registration of every person aged 3 and over in the area under investigation. The urine was tested with a specific glucose-reducing enzyme, and in positive cases blood glucose was examined. Cases with fasting level of more than 120 mg. percent in their blood were considered diabetics, and doubtful cases were subjected to the glucose-tolerance test.

In the non-Ashkenazic group we had a total of 1 percent diabetics in our population, 0.8 percent males and 1.1 percent females. For the Ashkenazic group we had a total of 2.5 percent, 1.7 percent males and 3 percent females. We may compare these figures with the results of studies made abroad (see Fig. 29). The percentage of diabetics varies from 0.26 in Iceland, 0.73 in Jamaica, and 1.5 in Mecklenburg, Germany, to 2.0 in Australia and 3.2 in New York. The prevalence determined by us in Ashkenazim is thus not so high as that of New York, whereas the non-Ashkenazim fall into the lower range of the series. These data do not justify the conclusion that the Jews in general are more prone to diabetes than other ethnic groups.

We were astonished to find that among the Yemenite Jews, the newcomers

5 Figures supplied by the Central Bureau of Statistics, Jerusalem.

6 Wilkerson, H. L. C., and Krall, L. P., Diabetes in a New England town, a study of 3,516 persons in Oxford, Mass., *J.A.M.A.*, *135*, 1947, 209-216.

had almost no diabetes. In examining about 5000 of them, we found only 3 cases. However, diabetes is common among Yemenites in Jerusalem, most of whom have been living in this city for more than 25 years. We therefore examined every Yemenite who had lived in Jerusalem for more than 25 years. Whereas the new immigrants had virtually no diabetes, the old settlers showed the same frequency as the Ashkenazim, and this applies to all age groups, including the 20-39 group. At the same time, Dr. Goldschmidt and Dr. Cohen were examining the Kurdish Jews in Maoz Zion, and together we examined 1000 new immigrants from

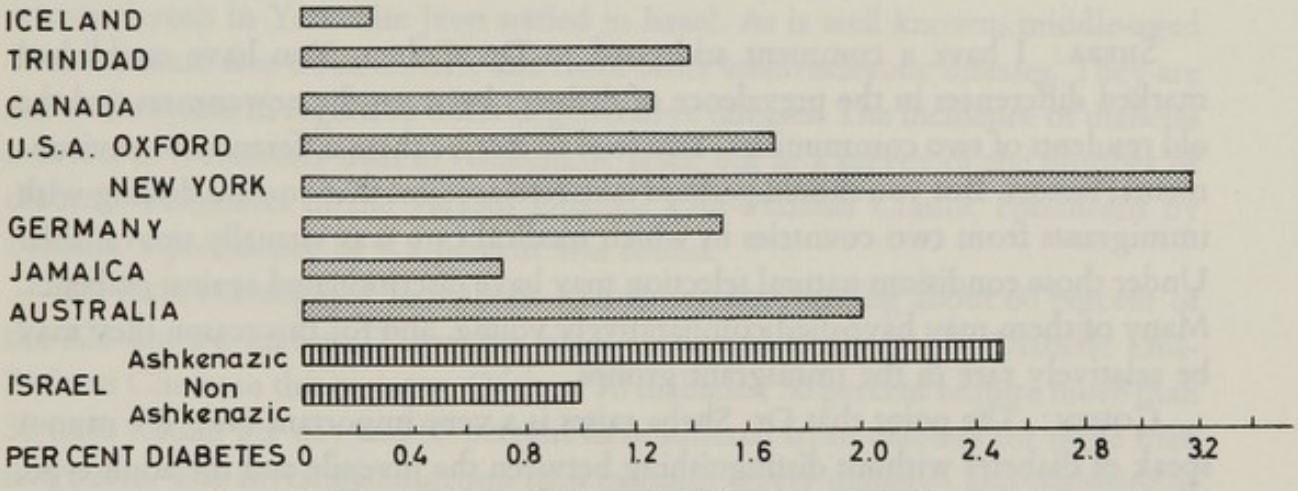


FIG. 29. The prevalence of diabetes in different countries. (Compiled from various sources listed by Cohen. See footnote 4).

Kurdistan. Among them, again, we found no diabetes. When we examined about 300 Kurdish Jews settled in Jerusalem for more than 25 years, diabetes among them was again as common as in Ashkenazim, about 2 percent being affected.

These data indicate that environment has a pronounced influence on the prevalence of diabetes. They do not deny the possible role of the genotype in diabetes, but they show definitely that environment is a very important factor in the etiology of this disease. In this connection it is of interest to compare the prevalence between males and females in the various communities. Although the non-Ashkenazim and the Ashkenazim show a higher prevalence in the female group, among Yemenites the male is more frequently affected. This again points to an environmental factor.

Before concluding, I should like to draw your attention to the role of the environment in determining the prevalence of another common disease—namely, arteriosclerosis. The data that I shall produce may be considered as supplementary to those of Prof. Ungar. It has already been stressed by Dreyfus[7] and by Toor, Katchalsky, *et al.*[8] that in Israel there is a difference in the prevalence of arteriosclerosis between old residents and new immigrants. But it is quite difficult to substantiate this theory because of the scarcity of pathological material. Together

[7] Dreyfuss, F., The incidence of myocardial infarctions in various communities in Israel, *Am. Heart J.*, *45*, 1953, 749-755.

[8] Toor, M., Katchalsky, A., Agmon, J., and Allalouf, D., Atherosclerosis and related factors in immigrants in Israel, *Circulation*, *22*, 1960, 265-279.

with Prof. Michaelson and Dr. Neumann,[9] we examined the retina in those two groups (see figure on page 320). The retina is eminently suitable for the direct examination of the blood vessels and their pathology. We admit that arteriosclerosis in the retina does not necessarily indicate the existence of arteriosclerosis in the vascular systems of other organs. It is, nevertheless, of great interest that the prevalence of involutionary sclerosis of the retina was much higher in subjects who had lived for at least 25 years in Israel than in new immigrants of corresponding age groups.

SHEBA: I have a comment addressed to Dr. Cohen. You have established marked differences in the prevalence of diabetes between the newcomers and the old residents of two communities. You tend to ascribe these differences to environmental factors. But you should perhaps take into account that you are dealing with immigrants from two countries in which medical care was virtually unavailable. Under those conditions natural selection may have discriminated against diabetics. Many of them may have died comparatively young, and for this reason they may be relatively rare in the immigrant groups.

COHEN: The point that Dr. Sheba raises is a very important one. We cannot speak of diabetes without distinguishing between the juvenile and the adult type. The data I presented relate to adult and not to juvenile diabetes. If you claim that none of the juvenile diabetics could be taken care of in, say, very primitive surroundings and they died, then I can see the point. But I cannot see how selection could play a role in a population group that reached the age of 30 without developing diabetes, came to this country, and was examined 10 years later, at the age of 40, at which age a certain percentage of diabetes is expected in our environment. This group is then compared with a similar age group which has lived in this country for more than 25 years. Or you can take a group of 40-year-olds among whom all diabetics had been eliminated by stringent selection in their country of origin. How would they be protected from developing diabetes at the age of 50 or 55? The most you can say is that you can expect a lower incidence, but not a zero incidence.

If you consider selection at work during several generations, it is important to remember that diabetes is a disease of middle and old age. It is quite possible that in the absence of medical care the life of a diabetic person was shortened by 10 or 20 years. But even if he died a premature death at 40 or 50, he may have left a good many children who could inherit his genetic predisposition to the disease. Selection against a disease with such late onset will therefore be quite inefficient.

STEINBERG: What proportion of the diabetics you examined knew of their disease?

9 Cohen, A. M., Neumann, E., and Michaelson, I. C., Involutionary sclerosis and diostolic hypertension, *Lancet*, 1961, 1050-1051.

COHEN: Clinically, you mean?

STEINBERG: Yes.

COHEN: We had about 40 percent of cases which were discovered by us.

STEINBERG: In both groups?

COHEN: Well, the newcomers had no diabetes; we had 3 cases in 5000. You cannot calculate proportions from such numbers. But among the population in general we had 40 percent who were discovered by us.

BRUNNER: I would like to add some remarks on the problem of diabetes and atherosclerosis in Yemenite Jews settled in Israel. As is well known, middle-aged Yemenites are free from C.A.D. and from other atherosclerotic diseases. They are not so fortunate in regard to other degenerative diseases. The incidence of diabetes is lower in Yemenites than in Ashkenazic Jews, but in a survey of the number of diabetic Yemenites in the various Diabetic Out-Patients Clinics, conducted by Nelken, a prevalence of 0.5 percent was found.

We have investigated 76 diabetic Yemenites, constituting about 60 percent of the 123 known diabetic Yemenites who are treated in the public Diabetic Out-Patients Clinics in this country. Of these 76 diabetics, 50 percent require more than 30 units insulin per day and 55 percent have suffered from diabetes for more than five years. The investigated group thus includes severe diabetics and diabetics of long standing. Sixty percent of the investigated subjects were men, and 40 percent were women. About 60 percent were older than 40 years, and nearly half were older than 50.

It is generally accepted that—*ceteris paribus*—diabetic patients suffer from atherosclerotic processes at an earlier age and in a more extensive and severe form than nondiabetics. However, in the Yemenite diabetics investigated,[1] we found only one case, of an old man, with myocardial infarction. No other incidence of ECG findings characterizing ischemic heart disease was detected. No case of peripheral vascular disease, diabetic nephropathy, or neuropathy was found. There were only a few patients suffering from diabetic retinopathy in the initial stage. This is a strikingly low incidence of occlusive vascular processes, as compared with the incidence of such conditions generally seen in diabetics of Western origin.

The lipid patterns of diabetic Yemenites were also investigated and compared with the lipids found in previous investigations in healthy Yemenites.[2,3] Yemenite lipid patterns are characterized by a rather low average cholesterol level, but it seems to us that the most important feature is the high percentage of α cholesterol

1 Brunner, D., Altman, S., Loebl, K., Nelken, L., and Reider, J., Occlusive vascular disease in diabetes. (In press.)

2 Brunner, D., and Loebl, K., Serum cholesterol, electrophoretic lipid pattern, diet and coronary artery disease: A study in coronary patients and in healthy men of different origin and occupations in Israel, *Ann. Int. Med., 49,* 1958, 732-750.

3 Brunner, D., Manelis, G., and Loebl, K., Influence of age and race on lipid levels in Israel, *Lancet, i,* 1959, 1071-1073.

(see p. 322). In young, middle-aged, and elderly Yemenites alike an average α-cholesterol percentage of about 27 to 29 was found. This is an important point, because it is a generally accepted opinion that the increase of serum cholesterol and of other lipid fractions with age is a regular biological process. In Yemenites, at least, there is no such increase of cholesterol.

A similar high level of α-cholesterol percentage was also found in young Ashkenazic Jews of the 18-20-year age group. On the other hand, the average α-cholesterol percentage of Ashkenazic middle-aged coronary patients is about 15 percent, whereas their mean total cholesterol level is higher than 250 mg. percent (see p. 322).

Several conclusions emerge from this study. There is a long-standing question as to whether diabetes produces earlier and more severe atherosclerosis or whether diabetes and atherosclerosis are two different but genetically associated diseases. The results of our investigation on diabetic Yemenites do not agree with either of these two assumptions. They show, on the contrary, that diabetes and atherosclerosis are not invariably associated. Yemenites may suffer from diabetes without developing vascular complications.

Nonetheless, a considerable proportion of diabetic Yemenites display atherogenic lipid patterns without showing overt occlusive vascular phenomena. It may be that a time factor is operating in these cases and that after a number of years overt atherosclerotic processes may appear.

In addition, other factors have to be considered—namely, the relative reluctance of Yemenites, even those suffering acutely from diabetes, to accept the diabetic diet, which is rather high in fats and proteins and low in carbohydrates; or the fact that Yemenites are generally not white-collar workers but laborers engaged in heavy manual work. All these questions call for further investigations.

NEEL: We have heard excellent presentations concerning diabetes and atherosclerosis in the various populations which can be studied in Israel. I think we can surmise that, with the rapidity of cultural change, new agents of selection are being introduced into our culture. On an intuitive basis we can perhaps doubt whether from the tactical standpoint we are going to find many situations as favorable as the sickle-cell-malaria situation for the study of natural selection. However, there will be some situations in which the opportunities will be more favorable than in others, and in this connection one cannot help being impressed by the rather remarkable situation in Israel.

Certainly Israel is characteristic of West European culture. But groups are being introduced who have been in an essentially Oriental culture—namely, the various non-Ashkenazic groups of Jews. One would wonder whether the genetic adjustment to the urbanized, mechanized culture of Western Europe that has occurred in the Ashkenazic group in the course of several hundred years may not be telescoped into a few generations in the non-Ashkenazic groups. In other words, there will be a rather intensive selective process brought to bear on these

groups. If this is the case, then the situation may be exceptionally favorable for study of the role of the various polymorphisms that we have been considering in susceptibility or resistance to all manner of disease and also for the study of genetic factors in such diseases as diabetes. We saw the curve indicating that the old Yemenite settlers are now developing a great deal of diabetes (see p. 325). One can prophesy that they will develop not only as much as the Ashkenazic group but perhaps even more, and then selection, even in these days of great medical care, will begin to make itself felt, because it is a fact that childhood diabetics seldom have a normal reproductive expectancy even today.

STEINBERG: I turn the Chair over to Dr. Ungar.

UNGAR: Dr. Steinberg will make some remarks on the papers we have heard before and some remarks which he has not disclosed to me and which are not contained in the official title of his presentation.

A. G. STEINBERG

Dependence of the Phenotype on Environment and Heredity

The title of my presentation is really another version of the title of this whole session. I shall discuss the interaction of the genotype with the environment in the production of two rather common conditions. The first of these is elevated serum cholesterol level. It is generally assumed that the genotype plays a minor role, if any, in the development of this condition. The second is cystic fibrosis of the pancreas, which is generally regarded as a straightforward Mendelian recessive. I shall attempt, among other things, to show the various pitfalls one encounters in estimating the frequency of a classical gene of this sort. I shall try also to demonstrate that gene frequencies have to be accurately determined before their dependence on selective agents can be studied.

In 1952, Adlersberg, Schaefer, and Drachman, of the Mt. Sinai Hospital in New York, and I reported a study based on a sample of approximately 500 consecutive admissions to the Mt. Sinai Hospital.[1] We were interested in the serum cholesterol level of these patients, having selected them only in the sense that they had no diseases known to cause an increase in serum cholesterol level.

At that time our definition of hypercholesterolemia was a level of total serum cholesterol greater than 279 mg. percent. Table I presents a summary of these findings. The population divided itself into almost equal groups, those of Jewish

1 Schaefer, L. E., Drachman, S. R., Steinberg, A. G., and Adlersberg, D., Genetic studies on hypercholesteremia: frequency in a hospital population and in families of hypercholesteremic index patients, *Am. Heart J.*, *46*, 1953, 99-116.

origin and those of non-Jewish origin, most of the latter being Puerto Ricans. It is seen that the frequency of hypercholesterolemia, defined as 280 mg. percent or higher, was much greater among the Jews than among the non-Jews, and that the difference in frequency is significant.

TABLE I

FREQUENCY OF HYPERCHOLESTEROLEMIA (SERUM CHOLESTEROL GREATER THAN 279 MG. PER 100 ML.) AMONG JEWISH AND NON-JEWISH PROBANDS*

		Hypercholesterolemic	
Proband	*Total*	*No.*	*%*
Jewish	266	56	21.0
Non-Jewish	212	19	9.0
Total	478	75	15.7

* From Schaefer *et al.* (see footnote 1).

TABLE II

FREQUENCY OF HYPERCHOLESTEROLEMIA (CHOLESTEROL LEVEL GREATER THAN 279 MG. PER 100 ML.) AMONG THE SIBLINGS AND CHILDREN OF JEWISH AND NON-JEWISH HYPERCHOLESTEROLEMIC PROBANDS*

	SIBLINGS			CHILDREN		
		Hypercholesterolemic			*Hypercholesterolemic*	
	Total	*No.*	*%*	*Total*	*No.*	*%*
Jewish	86	45	52.3	81	24	29.6
Non-Jewish	11	5	45.4	28	8	28.5
Total	97	50	51.5	109	32	29.4

* From Schaefer *et al.* (see footnote 1).

TABLE III

FREQUENCY OF HYPERCHOLESTEROLEMIA AMONG THE SIBLINGS AND CHILDREN OF THE HYPERCHOLESTEROLEMIC PROBANDS*

(Hypercholesterolemia defined by two different methods—A and B)

	A. KEYS ET AL.†			B. GREATER THAN 279 MG. PER 100 ML.		
		Hypercholesterolemic			*Hypercholesterolemic*	
	Total	*No.*	*%*	*Total*	*No.*	*%*
Siblings	78	29	36.2	97	50	51.5
Children	47	16	34.0	109	32	29.4

* From Schaefer *et al.* (see footnote 1).
† See footnote 2.

From this group of patients we selected those who by our definition had hypercholesterolemia, and we followed as many of their sibs and children as we could. Table II indicates that the frequency of hypercholesterolemia among the sibs and the children of individuals with hypercholesterolemia was higher than in the unselected population and that this was true regardless of whether the proband (index patient) was of Jewish or non-Jewish origin.

We reanalyzed the family data using the standards for adult middle-class males in Minnesota, published by Keys *et al.*[2] Although we realized that these standards

2 Keys, A., Fidanza, F., Scardi, V., and Bergami, G., The trend of serum cholesterol levels with age, *Lancet, ii,* 1952, 209-210.

were not strictly applicable to our sample, which was composed of both males and females who were poor and of different ethnic origin from the middle-class males studied by Keys *et al.*, it seemed to us that these levels, changing with age, would be a better approximation to the data than a fixed level. The results of this reanalysis (without regard to ethnic origin), along with the results obtained using a fixed level, are shown in Table III. The frequency of hypercholesterolemia is the same in the sibs and offspring (Table III, A.), being about 35 percent. These observations suggest that there may be a genetic component involved in the causation of elevated serum cholesterol levels. The results could be interpreted on the basis of a single dominant gene with incomplete penetrance. We offered this simplified interpretation merely as a tentative suggestion.

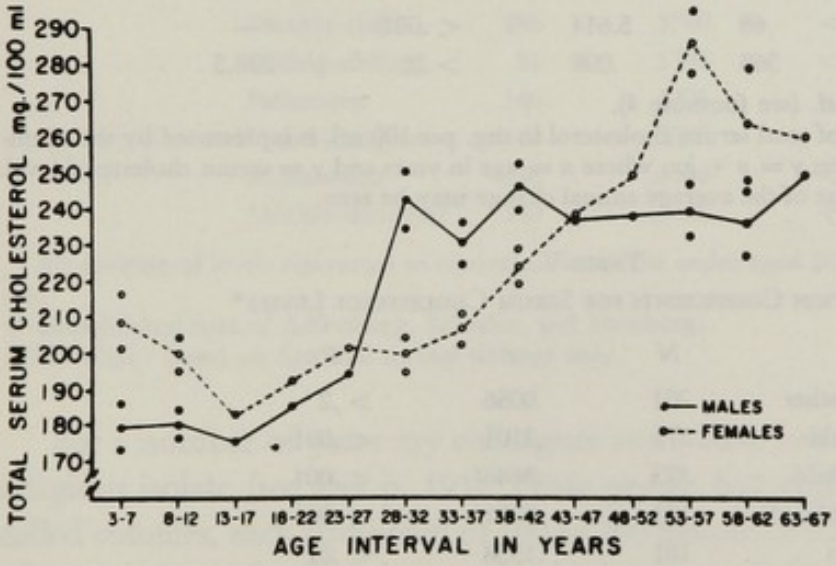


FIG. 30. Total serum cholesterol levels by age in males and females. From Adlersberg *et al.* (see footnote 3).

We then sampled a population living on Staten Island, composed of individuals who were members of the Health Insurance Plan of New York.[3,4] They were selected without regard to health or cholesterol level since all that was required for them to be insured was that the head of the family be a member of a trade union which had arranged for this insurance program. Blood samples were taken when the families came for their annual physical examination.

Figure 30, based on the results of these studies, shows the change of serum cholesterol level with age and with sex. A sharp rise in serum cholesterol level begins in males between the ages of 20 and 25 years. The rise, 5.6 mg. percent per year, continues to about age 35. Thereafter the serum cholesterol level remains essentially constant. In females, the level seems to remain constant until about the age of 35 years and then rises, at the rate of about 3 mg. percent per year, to about the age of 60. At still higher ages this level appears to remain constant so far as we could judge from the limited number of older women represented in our sample.

[3] Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang, C. I., Age, sex, serum lipids, and coronary atherosclerosis, *J.A.M.A.*, *162*, 1956, 619-622.

[4] Schaefer, L. E., Adlersberg, D., and Steinberg, A. G., Heredity, environment, and serum cholesterol, *Circulation*, *17*, 1958, 537-542.

Table IV shows the regressions of cholesterol level on age. We used these regression coefficients to calculate the expected values and their standard deviations. All serum cholesterol levels were then converted to levels equivalent to those for males aged 20, thereby eliminating variation due to age and sex. Using these

TABLE IV

CHANGES IN SERUM CHOLESTEROL LEVEL WITH AGE IN A STATEN ISLAND POPULATION*

Age	*N*	*b*†	*P*‡	*Mean*
		FEMALES		
2-32	312	—.019	> .2	196.8
33-58	304	2.990	< .001	—
		MALES		
2-19	184	—.471	> .2	178.2
20-32	68	5.614	< .001	—
33-60	368	.008	> .2	238.3

* Modified from Schaefer *et al.* (see footnote 4).
† The average annual change of total serum cholesterol in mg. per 100 ml. is represented by the coefficient b in the regression equation $y = a + bx$, where x = age in years and y = serum cholesterol level.
‡ Probability that the true value of the average annual change may be zero.

TABLE V

CORRELATION COEFFICIENTS FOR SERUM CHOLESTEROL LEVELS*

	N	*r*	*P*
Mother-father	201	.0056	> .2
Father-child	373	.2101	< .001
Mother-child	373	.3646	< .001
Sibling-sibling†	123	.3701	< .001
Father-son	181	.1558	< .01
Father-daughter	192	.2616	< .001
Mother-son	181	.3402	< .001
Mother-daughter	192	.3903	< .001

* Modified from Schaefer *et al.* (see footnote 4). All cholesterol levels converted to equivalent levels for males aged 20 to eliminate factors of age and sex.
† Intraclass r based on first and second siblings only.

converted values, we calculated the correlation coefficients between husband and wife, and between parents and offspring (Table V). The coefficient of correlation between husband and wife is not different from zero, whereas those between parents and children and between sibs are significantly different from zero. All these people share meals and a common environment, but only the sibs, and the parents and their children, have common genes. Since the only significant correlations occurred between blood relatives, we concluded that a genetic component may be involved in the determination of cholesterol level. This is supported by the observation that the frequency of hypercholesterolemia among the offspring is greater if one parent is hypercholesterolemic than if neither is affected and vice versa; the frequency of hypercholesterolemia is greater among parents of hypercholesterolemic probands than among parents of normocholesterolemic probands.

But the mode of inheritance does not follow any recognizable simple genetic pattern.[5]

Table VI lists the correlation coefficients calculated (from data treated as they were for the Staten Island group) for a population from Manhattan. This population is almost entirely Jewish, whereas that of Staten Island is almost entirely non-Jewish. Again significant correlations were found only between blood relatives.

TABLE VI
CORRELATION COEFFICIENTS FOR SERUM CHOLESTEROL LEVELS*
NEW YORK FAMILIES†

	N	*r*	*P*
Mother-father	204	.0216	> .70
Father-child	286	.4205	< .001
Mother-child	286	.5760	< .001
Sibling-sibling‡	81	5765	< .001
Father-son	146	.4725	< .001
Father-daughter	140	.3562	< .001
Mother-son	146	.6046	< .001
Mother-daughter	140	.5636	< .001

* All cholesterol levels converted to equivalent levels for males aged 20 to eliminate factors of age and sex.
† Unpublished data of Adlersberg, Schaefer, and Steinberg.
‡ Intraclass *r* based on first and second siblings only.

For a number of years my colleagues and I have been studying an Anabaptist religious isolate (see also p. 193). These people live communally on large farms called colonies, each composed of 100 to 200 people. A colony, which may consist of ten to twenty families, has one kitchen and two dining rooms, one for those 15 years of age and older and a second for those under 15. In both the children's and adults' dining rooms, males eat at one long table and females at another. Hence there is no familial pattern of eating. Although each member of the colony is offered the same food, obviously not everyone consumes the same food. However, it is necessary to emphasize that all meals are eaten together by all individuals in the colony. It should be noted that there is no economic differential in this society, whose structure is entirely communal, based on principles of the New Testament.

We thought it would be interesting to compare the correlation patterns of the serum cholesterol levels in this population with a remarkably uniform environment for all members of a colony with those of the populations of Staten Island and Manhattan. The correlation coefficients (Table VII) follow precisely the same pattern as in the noncommunal populations. Note that although in the isolate husband and wife have grown up in essentially the same environment and have shared the same nutritional pattern all their lives, not only since they were married, there is no significant correlation between their cholesterol levels.

5 *Ibid.*

However, a difference between the members of the religious isolate and other groups emerged when we estimated the regression coefficients (Table VIII). The pattern for males was identical with that of the previous populations sampled. The difference lay in the regression of serum cholesterol level on age for women. Whereas in the females of the three previous surveys the rise in cholesterol level sets in later and endures for a longer time than in the males, in the isolate group the female pattern is very similar to that of the male.

TABLE VII

CORRELATION COEFFICIENTS FOR SERUM CHOLESTEROL LEVELS AMONG FAMILY MEMBERS OF A RELIGIOUS ISOLATE*

	N	*r*	*P*
Father-mother	173	.0488	~ .525
Father-child	732	.1584	< .001
Mother-child	804	.1829	< .001
Father-son	364	.1851	< .001
Father-daughter	368	.1386	< .01
Mother-son	392	.3183	< .001
Mother-daughter	412	.1300	< .01

* Unpublished data (1958 and 1959), Steinberg and Adlersberg.

TABLE VIII

CHANGES IN SERUM CHOLESTEROL LEVELS WITH AGE IN MEMBERS OF A RELIGIOUS ISOLATE*

Age	*N*	*b*†	*P*†	*Mean*
		FEMALES		
7-21	331	.745	> .10	182.7
22-34	135	3.526	< .001	—
35-81	108	.808	> .05	242.6
		MALES		
5-21	308	— .482	> .20	176.7
22-35	112	3.616	< .001	—
35-78	137	.355	> .20	234.8

* Unpublished data (1958 and 1959), Steinberg and Adlersberg.
† For explanation of symbols *b* and *P* see Table IV.

We have no explanation for this, but it should be noted that in this population the wife becomes pregnant almost immediately after marriage and thereafter is either lactating or pregnant until menopause. This unusual hormonal activity may account in part for the fact that in this population the pattern of serum cholesterol level of females is like that of males.

I should also point out that mortality rate and total life expectancy of the males in this population is identical with that of other males who live in the same part of the United States, whereas the life expectancy of the women is different from that of other females, being essentially the same as that of the males. There is, therefore, no sex difference in cholesterol level or in life expectancy in this community.

It was by chance that I chose cystic fibrosis of the pancreas (CF) as the second

instance of gene-environment interaction to discuss at this conference. I am pleased that I did so, because similar studies are now in progress in this country (see p. 294). CF is believed to be a recessively inherited disease with an extraordinarily high frequency among Caucasoids. It apparently does not occur among Negroids with no white ancestry. Only a short time ago this disease was entirely lethal, generally before the age of ten. Recent advances in medical care of affected children have extended their life expectancy considerably, indicating considerable interference of the environment with the expression of this gene.

Two reports[6,7] had indicated that the disease was at least as frequent as one in a thousand, thus posing the problem of how this lethal gene maintains itself in the population at so high a frequency. Two possibilities, not mutually exclusive, are mutation and heterozygote advantage.

If the frequency were, indeed, as great as one in a thousand (gene frequency approximately .03), it might be possible to measure heterozygote advantage by selecting appropriate families. Unless the mutation rate were unusually high, a heterozygote advantage of about 3 percent would be required to maintain the gene at a frequency of .03. Disregarding mutations, we may assume that both parents of an affected proband are heterozygotes, each inheriting the gene from one of his own parents. In the grandparental generation we would have two matings of a heterozygote with a normal homozygote.

This is true of more than 90 percent of the grandparental couples, even if CF is as frequent as one per thousand. Hence, we have for each child two completed families resulting from the mating of a heterozygote with a normal individual. Since CF did not occur among the children of these grandparental matings, it could not be a cause for limiting family size. Using these families we could determine the mean family size in such matings and compare it with the mean family size of an appropriate set of controls. The sample would have to be large, even though the frequency of the homozygous recessive were as great as one in a thousand. Since the level of heterozygote advantage required to maintain the gene and the size of the sample necessary to detect this advantage depend on the frequency of the homozygous recessive, we decided to redetermine the frequency of the gene before undertaking the study. We based our study on the population of the state of Ohio.[8]

Death certificates (not coded summaries) for all white children born during the years 1950 to 1953 inclusive were examined. If CF or any one of some thirty items was entered on the death certificate, it was copied. If CF as such was not recorded on the death certificate, a transcript of the hospital record was obtained if the child

6 Andersen, Dorothy H., and Hodges, R. G., Celiac syndrome V. Genetics of cystic fibrosis of the pancreas with a consideration of the etiology, *Am. J. Dis. Child., 72,* 1946, 62-80.

7 Goodman, H. O., and Reed, S. C., Heredity of fibrosis of the pancreas. Possible mutation rate of the gene, *Am. J. Human Gen., 4,* 1952, 59-71.

8 Steinberg, A. G., and Brown, D. C., On the incidence of cystic fibrosis of the pancreas, *Am. J. Human Gen., 12,* 1960, 416-424.

had died in a hospital, or of the autopsy report if a post-mortem examination had been made. If such records were not available, the diagnosis on the death certificate was accepted.

The death certificates for the counties including the cities of Columbus (Franklin) and Cincinnati (Hamilton) were checked twice by two different teams. The death certificates for the county including Cleveland (Cuyahoga) were checked three times (once in the county and twice at the State Records Office in Columbus) by three different teams. Those for the remainder of the state were examined only once. The checks showed that oversights were negligible.

All pediatricians in Ohio were asked by mail, and if necessary by telephone, to supply us with the *names, birth dates, and, if dead, date of death* of all their patients with CF who had been born during the years 1950 through 1953. The response was 100 percent. Similar data were requested of all major hospitals in the state, and of all hospitals in Cuyahoga County. Again, the response was 100 percent.

We divided the state into four groups, because in the counties which include Cleveland, Columbus, and Cincinnati, there are large medical centers with pediatricians interested in CF, whereas the rest of the state is agricultural and has fewer pediatricians and no medical centers interested in CF. Initially, I assumed that we might find a higher reported incidence in the three counties with well-developed medical centers than in the other areas of the state; this is why the data appear in four groups.

The study, which was begun in the fall of 1957, was based on white infants born alive in Ohio during the years 1950 through 1953. This gave us a known base line for comparison. There were about three-quarters of a million live births of white children during this period. As already indicated, the causes of death were all confirmed by death certificates and in many cases by autopsies. The diagnoses of the living patients were confirmed through hospital records.

Table IX indicates that, contrary to expectation, the incidence of cystic fibrosis of the pancreas was essentially the same in all four regions. The frequency for the entire sample is approximately 1 in 3700. This is considerably lower than the previously reported frequencies but compares well with the 1 in 4500 reported for Israel (see p. 294).

The estimated gene frequency (~ 0.016) is so low that the reproductive advantage necessary to maintain the gene even in the absence of mutation is too small to be demonstrated except in a sample of forbidding dimensions. Thus it no longer appeared feasible to look for increased reproductive rates of heterozygotes.

As pointed out above, pedigree data indicate that CF is due to a recessive gene, but this need not always be the same recessive gene. It is possible that homozygosis for genes at different loci leads to the same clinical entity, and we would never detect it by the usual method of collecting family data.

Some years ago I developed a method[9] which might reveal whether we were

9 Steinberg, A. G., Population genetics—special cases, in Burdette, Walter J. (ed.), *Methodology in Human Genetics*, Holden-Day, San Francisco, 1962.

dealing with one or several loci. If the frequency of a recessive gene causing cystic fibrosis is q_i where i represents any particular gene, then q_i^2 would be the frequency of the homozygote. Since there may be many such genes, $\Sigma q_i^2 = g$ would be the frequency of the homozygotes for these genes in the general population. The frequency (c) with which the first cousins of probands would be expected to have

TABLE IX

INCIDENCE OF CF PATIENTS AMONG WHITE CHILDREN BORN ALIVE IN OHIO DURING THE YEARS 1950 THROUGH 1953*

	Cuyahoga County	*Franklin County*	*Hamilton County*	*Remaining Counties*	*Entire State*
Live Births	122,090	49,296	65,940	504,837	742,163
CF patients	31	19	17	131	198
Incidence of CF:					
1 in:	3,938	2,595	3,879	3,854	3,748
as decimal	.000254	.000385	.000258	.000260	.000267
95% Confidence intervals:					
Upper	.000307	.000494	.000335	.000284	.000287
Lower	.000191	.000254	.000163	.000233	.000245

* From Steinberg and Brown (see footnote 8).

the disease equals $\frac{1}{4}\overset{k}{\Sigma} q_i + (k-1)\overset{k}{\Sigma} q_i^2 = c$, where, as before, q_i is the frequency of the individual genes and k is the number of loci involved. It is assumed that few if any doubly or trebly homozygous individuals occur and that multiply heterozygous individuals are normal.

If it is assumed that the variance of q is small relative to $\bar{q}^2$, where $\bar{q}$ is the mean frequency of q, we may express c and g in terms of k and $\bar{q}$ as follows:

$$c = \tfrac{1}{4}k\bar{q} + k(k-1)\bar{q}^2 \quad (1)$$

$$g = k\bar{q}^2 \quad (2)$$

These simultaneous equations may be solved for k and for $\bar{q}$ in terms of the observed values, c and g.[10]

If g, the frequency of a disease in a population, is known or assumed, we can assume values of k and solve equation (1) for c. We have done this, using the frequency of CF derived for the population of Ohio, and have compared the derived values of c with the frequency we have observed among cousins of a series of probands. The work is still in progress. Among the first 1084 cousins we examined, 6 had the disease, giving a frequency of roughly 5 per 1000. This is close to the expected frequency based on $k = 2$ (0.00602) and is significantly different from the expected value based on $k = 1$ (0.00407), but more data are required to establish that two loci are involved. If two or more loci can be demonstrated to cause CF, intensive studies to distinguish the different entities would be warranted. If separation of different types should prove feasible, better understanding and care of the disease could follow.

10 *Ibid.*

I have attempted to show that genetics plays an important role in the determination of a character (serum cholesterol level) which is generally believed to be essentially under environmental control and that the expression of a character (CF) clearly under genetic control is certainly influenced by manipulation of the environment. Finally, I have offered a method for ascertaining the number of loci involved in the determination of an autosomal recessive lethal character.

Incidentally, although we have shown that in Ohio cystic fibrosis is only one-quarter as frequent as is generally assumed for Caucasian populations, it still is far more common than in nonwhites, in whom the disease is almost nonexistent. It is tempting to ascribe this difference in gene frequencies to different viabilities of heterozygotes in diverse environments. However, I have refrained from offering any such interpretation and from venturing to explain the role of hypercholesterolemia in atherosclerosis.

HIRSCHHORN: I should like to comment briefly on some of the statements that were made about atherosclerosis this afternoon.

In several studies in the United States, in Africa, and some other countries, it has recently been discovered that the correlation between coronary atherosclerosis and cholesterol level is not very high. On the other hand, when another fat fraction in the blood was measured—that of the triglyceride or neutral fat, which makes up the bulk of the fat that we consume—the correlation was extremely high.

Some years ago in Sweden at Prof. Böök's Institute, we did a population study[1] on a thousand students at Uppsala College and found an elevation of serum triglyceride in approximately 3 percent of these totally asymptomatic persons. We are now repeating this study in the United States and appear to be coming up with an approximately similar incidence in the United States. Since this elevation of serum triglycerides is, in fact, associated with coronary atherosclerosis, the underlying metabolic disturbance is of great interest.

The chylomicron is that fraction of the serum which carries most of the triglycerides after ingestion. These are broken down by an enzyme called lipoprotein lipase, which is activated by heparin, and the free fatty acids are then carried off to be metabolized. Two of the possible defects in this mechanism, first, absence or diminution of enzyme and, second, improper activation of the enzyme by heparin, have been found and seem to be inherited in a very straightforward manner.[2]

These defects may be discovered by a rather simple method. One feeds an individual a rich fat meal and follows the triglyceride in his blood. At 12 hours there is an excellent discrimination point. If one takes a zero and a 12-hour sample, or even only the 12-hour sample, the abnormal hyperlipemic individual may easily be distinguished from the normal.

We have studied families with typical hyperlipemia and have followed the

[1] Hirschhorn, K., Hirschhorn, R., Fraccaro, M., and Böök, J. A., Incidence of familial hyperlipemia, *Science, 129,* 1958, 716-717.

[2] Sklarin, B. S., Seegers, W., and Hirschhorn, K., Hyperlipemia, *Geriatrics, 16,* 1961, 374-381.

abnormal gene through three generations of heterozygotes. The homozygous condition has appeared in one family. This is a rather severe disease in children, frequently causing death before puberty.

It is not understood why the incidence of homozygous hyperlipemia should be relatively low. Perhaps it is often misdiagnosed. But I have a feeling that at least two and probably several more loci may be responsible for the typical symptoms of hyperlipemia. Homozygosity at a single locus may be insufficient to produce the full syndrome.

Different types of the disease may be distinguished by administration of heparin to affected individuals. Some will respond very rapidly with a lowering of their triglyceride, whereas others are completely resistant to heparin. We have evidence of genetic variation in the lipid-carrying proteins of the blood. With paper electrophoresis we were able to demonstrate an abnormal double band in the β-1 lipoprotein area in three generations of a family.[3] There is also a rumor of a family with inherited absence of α lipoproteins.

In closing I would like to urge that any survey study in relation to atherosclerosis and lipids try to include tests for triglycerides of one sort or another, since this does seem to be the most important factor associated with atherosclerosis.

STEINBERG: Dr. Rubin has some data on tests which may help the geneticists solve a problem on which many have spent some years working without success.

C. E. RUBIN

Environmental Effects on the Manifestation of Celiac Sprue

I would like to talk to you about celiac sprue, a disease that has been discussed at length with respect to its possible hereditary aspects. One has to be able to make a diagnosis in an objective way in order to investigate the possible genetic nature of disease; preferably one should be able to make the diagnosis in its subclinical form. It is especially pertinent to describe to you the small-bowel biopsy method of diagnosis in celiac sprue because the manifestation of the illness is so clearly related to environmental factors, which, in turn, are dependent on genetic ones.

This disease is variously known as idiopathic sprue, idiopathic steatorrhea, gluten-induced enteropathy, adult celiac disease, etc. It is characterized by a primary inability to absorb various nutrients, especially lipids. In Holland, during World War II, Dicke, Weijers, and Van de Kamer[1] intuitively and ingeniously realized

3 Seegers, W., Weiner, L. B., and Hirschhorn, K., Genetically determined variant of human beta lipoprotein, *Circulation, 24,* 1961, 403–404.

1 Dicke, W. K., Weijers, H. A., and Van de Kamer, J. H., Celiac disease. II. The presence in wheat of a factor having a deleterious effect in cases of celiac disease, *Acta paediat., 42,* 1953, 34–42.

that the marked lowering of incidence of this disease in their country might well be related to the fact that the Nazis had stolen their grain and therefore removed it from their diet. Actually, in practice it turned out that the removal of wheat, rye, and barley from the diet was a very effective therapeutic measure, resulting in marked amelioration of the illness.

Most textbooks of medicine state, erroneously, that one of the remarkable features of this illness is the pronounced functional abnormality of the small intestine in the face of its normal morphological appearance. Actually, it is not anatomically normal but rather it has a characteristic abnormality which enables accurate diagnoses to be made by means of a suction biopsy tube in ambulatory patients. This abnormality was missed at post-mortem examination because of the rapid autolysis of the intestinal mucosa, which distorts it and makes diagnosis impossible. Now that small-bowel biopsies may be taken safely and with very little discomfort, beautiful histologic material is available and the abnormality in celiac sprue is obvious. The normal biopsy is usually about 3 mm. in diameter and is covered with numerous delicate fingerlike villi which may be easily recognized with a hand lens. The diagnostic biopsy in celiac sprue is devoid of villi or has a few present which are markedly blunted and shortened.[2] In carefully oriented sections the characteristic loss of villi is obvious histologically (Fig. 31A); in Figure 31B, one can see a normal control for contrast. Incidentally, cystic fibrosis, which is confused with celiac sprue, shows a normal biopsy because it is primarily a pancreatic malfunction rather than a primary intestinal disease.

Characteristically, celiac disease disappears as the child grows up, and pediatricians refer to cured celiac disease. If the environmental factor of dietary gluten is present, the patient should continue to manifest the genetic marker of an abnormal intestinal mucosa. In our opinion celiac sprue is an inherited inability to handle grain protein in a normal fashion, with the result that the gut is injured when these grains are ingested. The jejunal biopsy was abnormal in an 18-year-old girl who felt well when biopsied although she had suffered from severe celiac disease in childhood. She was eating a normal diet containing gluten, but despite her external appearance of well-being she exhibited the internal evidence of gluten injury in her intestine. Any patient with celiac disease who is taking a normal diet containing gluten will manifest this lesion.

If one withdraws the offending environmental agents by a suitable gluten-free diet, the small bowel may recover completely. Figure 32A illustrates an abnormal biopsy in a 2½-year-old celiac; Figure 32B shows the regression toward normal, three-quarters of a year later while the patient was on a strict gluten-free diet. If, as a result of a gluten-free diet, the bowel has become normal, it can be made

[2] Rubin, C. E., Brandborg, L. L., Phelps, P. C., and Taylor, H. C., Jr., Studies of celiac disease: I. The apparent identical and specific nature of the duodenal and proximal jejunal lesion in celiac disease and idiopathic sprue, *Gastroenterology, 38,* 1960, 28–49.

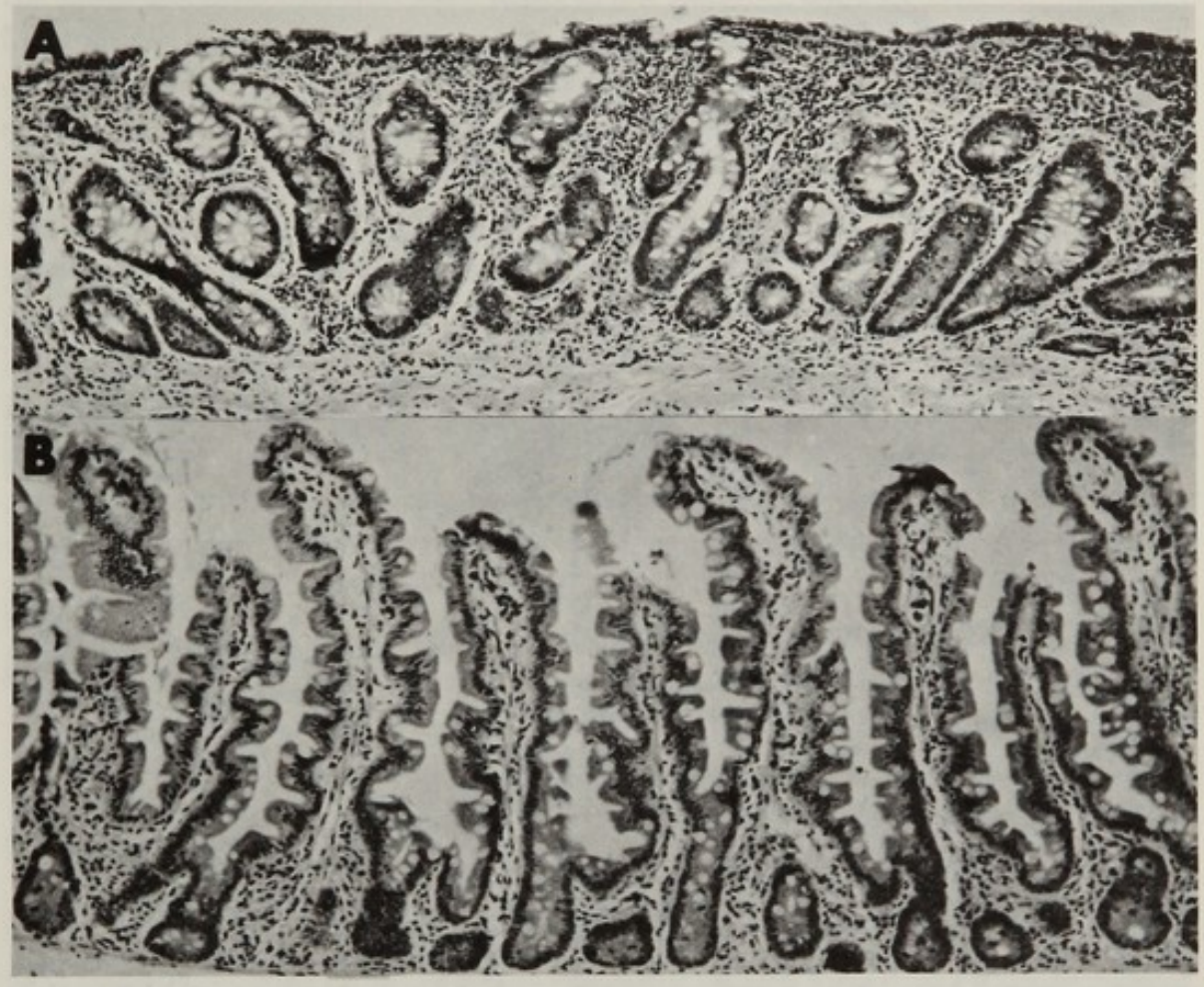


FIG. 31. Sections of jejunum biopsies in a case of celiac sprue (A) and in a normal control (B).

abnormal within hours by exposing it to gluten, and this has been demonstrated unequivocally in man.[3]

Dr. Walter MacDonald, in our laboratory, has begun a systematic study of the genetic aspects of this disease, using the small-bowel marker. In the course of our study on the pathogenesis of this illness we have long suspected that it might be genetic because the disease and the characteristic biopsy have been observed by us in identical twins and in several successive generations. Further work remains to be done if the exact mode of inheritance is to be determined.

WAISMAN: I would also like to comment on the importance of environmental factors in the manifestation of inherited conditions. One of the things which has interested me a great deal as a biochemist who is also a pediatrician is the variance due to environmental factors that we see in many childhood diseases. We certainly

3 Rubin, C. E., Brandborg, L. L., Flick, A. L., Parmentier, C. M., Phelps, P., and Van Niel, S., The, effect of wheat instillation into the proximal ileum of patients with idiopathic sprue, *J. Clin. Invest.*, *39*, 1960, 1023.

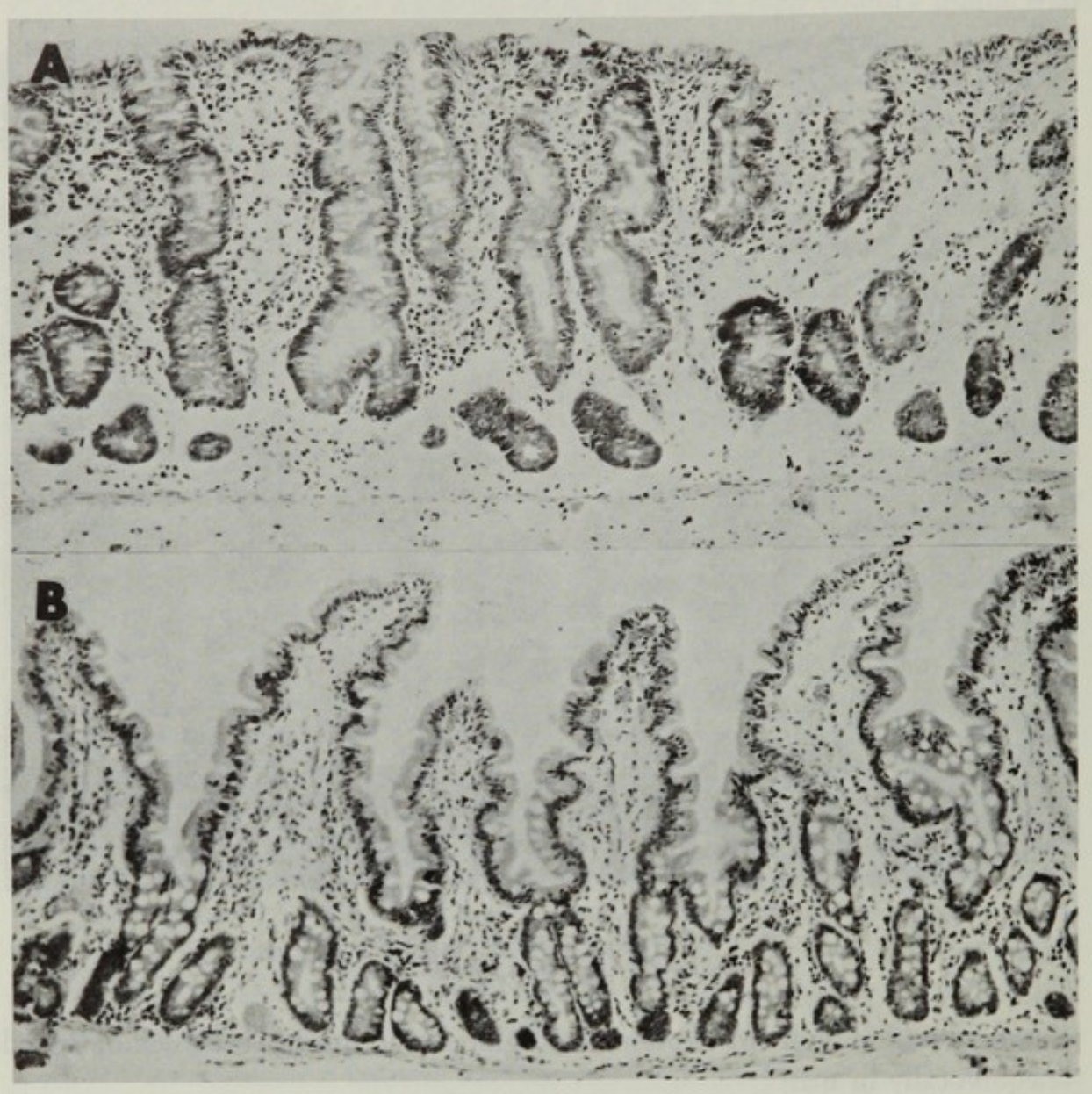


FIG. 32. Sections of jejunum biopsies of a three-year-old girl on a normal diet (A) and on a gluten-free diet (B).

have a genetic environment, about which we have heard a great deal during the last few days, and we certainly have a nutritional environment which alters circumstances. We have also a biochemical environment, and it may be that all three of these are very closely related.

The biochemical environment may be either favorable or unfavorable. I would like to point out that in phenylketonuria, for example, we change the environment when we treat an affected child whose disorder we have diagnosed early. We alter his environment simply by giving him a low-phenylalanine diet. In these circumstances we bypass his enzymatic defect, which is due, of course, to his gene defect. After a child is removed from a low-phenylalanine diet, the phenylalanine rises in his blood again and one can ask: Can his brain still be damaged at this stage by the high blood phenylalanine or its by-products? In other words, the fact that

the brain has now matured may make it less liable to damage than an immature brain. So the question is always: How long do you keep a PKU child on a low-phenylalanine diet? There are still not enough data to answer this fully.

Although it appears that, once the brain has matured, it is less likely to be damaged by phenylalanine metabolites, individual differences in brain susceptibility to injury may well be genetic. We have some data which would appear to be indirect but may be helpful. There are some untreated phenylketonurics with high phenylalanine, high excretion of the usual products in the urine, but normal intelligence. If you take the blood level in some of these PKU children who have normal I.Q., you find consistently high blood-phenylalanine levels. Nevertheless some of these patients have a certain low level of phenylalanine-hydroxylase activity in their livers. A spectrum varying from 0 to 100-percent enzyme activity appears to exist. PKU patients differ in their enzyme activities and therefore in their ability to respond to a low-phenylalanine diet.

One final word about what our biochemical knowledge can lead to. Our improved methods of treatment, as in phenylketonuria, may allow us to interfere with the natural course of events. If we manage to improve enough children who are phenylketonuric so that they ultimately marry and have children of their own, there will certainly be more phenylketonuric patients in the future generations. This is a troublesome question which merits serious consideration since we are on the threshold of many advances in the treatment of biochemical disorders which will increase the genetic load of the population.

MOTULSKY: In considering various environmental factors interacting with genetic diseases, we have come across an interesting example of climatic interaction. The fact that hereditary spherocytosis or acholuric jaundice is much rarer in Negroes than in Northern populations caused us to wonder whether climate might not have something to do with this. It is well known that the red cell of affected subjects is highly susceptible to heat *in vitro*. One of the tests for the disease is exposure of the erythrocyte to a hot environment, where the cells of affected individuals will lyse rapidly. In our laboratory we have a Peromyscus strain which has a disease homologous to acholuric jaundice in man—hereditary spherocytosis. We put these mice in hot chambers at 30°C. and found that within two weeks half of them died with severe hemolytic crises, suggesting that in a hot environment this gene is at a marked disadvantage. Ordinarily these mice come from the northern United States—Oregon and Washington.

Returning to cystic fibrosis, one wonders whether the marked difference between Negro and white populations in the incidence of this disease might not have a similar basis. One of the criteria of cystic fibrosis, increased excretion of sodium chloride in the sweat, was discovered when considerable numbers of homozygotes with cystic fibrosis died during the very hot weather in New York. Now, it is known that at least half or more of the heterozygotes for cystic fibrosis do have trouble with sweat secretion. Is it possible that this particular

expression of the gene might be a disadvantage in a hot climate and that this might be the reason why in Africa this gene has never reached the frequency observed in Caucasoid populations?

STEINBERG: I want to take just a minute to discuss the last point. We considered this some time ago. Actually the elevation in the sweat electrolytes in the heterozygotes is relatively slight, and most of them are well within the normal range of excretion. I therefore doubt seriously whether this could be the differential factor between the two groups.

LEVIN: I would like to add to Dr. Motulsky's remarks on natural selection in fibrocystic disease of the pancreas. This may come in conflict with some of your remarks, Dr. Steinberg. I believe that environment may have an important effect on sufferers from this disease in the tropics and subtropics, particularly among the underprivileged peoples of the world. It is in this large group that fibrocystic disease of the pancreas is so rarely seen. It is also in this group that infantile gastroenteritis is such a problem and the mortality from this condition so immensely high. We suggest the possibility that the full-fledged case of fibrocystic disease of the pancreas, with its tendency to greater losses of electrolytes, especially in hot weather, may not survive the attacks of infantile gastroenteritis with its extra burden of electrolyte losses.

We have been studying this aspect of natural selection in fibrocystic disease of the pancreas at the Kaplan Hospital in Rehovot during the past year.

STEINBERG: Dr. Levin, are you referring to selection against homozygotes or against heterozygotes? My point was that the heterozygotes have as a rule only a slight impairment of the ability to conserve electrolytes. Since the vast majority of the mutant genes are carried in heterozygotes, this mode of selection cannot be very important.

MOTULSKY: Is it not possible that even a slight difference in selective advantage in a hot environment might carry the balance in a situation such as that?

STEINBERG: Dr. Tanaka has some interesting data comparing the frequencies of common hereditary diseases and malformations between Caucasians and Japanese, and I wonder if he would be good enough to tell us about these data now.

KATUMI TANAKA

Differences Between Caucasians and Japanese in the Incidence of Certain Abnormalities

The incidence of numerous abnormalities varies among ethnic groups. Several speakers at this meeting have stressed that environmental as well as genetic factors may be responsible for such differences. Of course, this problem does not arise as

long as we concentrate on fully penetrant characters with simple Mendelian inheritance. But when we turn to abnormalities with variable penetrance and expressivity and especially to the congenital malformations that are entirely heterogeneous in origin, we can no longer be certain that ethnic differences in the incidence of these characters have a truly genetic basis. I should like to illustrate this point by reference to some abnormalities which are either more common or rarer in the Japanese people than in Caucasians.

The manifestation of the various types of color blindness is apparently quite independent of the environment, and the incidence of these abnormalities in any ethnic group is therefore directly related to the frequencies of the abnormal genes.

The frequency of color blindness among Japanese males has been reported[1] to be lower than 5 percent, in contrast to about 8 percent among Western males. The incidence of the four major types of color blindness appears to be different as well. Whereas deuteranopia is about as common in Japanese as in Caucasians, the other three types are much rarer. In particular, deuteranomaly is less than half as frequent

TABLE I

THE FREQUENCIES OF THE FOUR TYPES OF COLOR BLINDNESS AMONG MALES OF VARIOUS POPULATIONS

Country	*Total %*	*Protanomaly*	*Protanopia*	*Deuteranomaly*	*Deuteranopia*	*Deuteranomaly : Deuteranopia*
			CAUCASIAN SAMPLES			
Norway[2]	8.01	1.04	0.88	5.06	1.03	4.94
Switzerland[3]	7.95	0.60	1.60	4.25	1.50	2.83
Switzerland[4]	8.0	0.80	1.40	4.50	1.30	3.43
Germany[5]	—	—	—	—	—	3.67
Germany[6]	7.75	0.68	1.09	4.01	1.97	2.04
England[7]	8.82	1.27	1.27	5.08	1.20	4.24
Belgium[8]	8.37	1.01	0.94	4.92	1.48	3.32
			JAPANESE SAMPLES			
Japan[9]	4.71	0.51	0.38	2.18	1.76	1.25
Japan[10]	4.39	0.50	0.17	1.99	1.74	0.88

1 Nakajima, A., *et al.*, Distribution of eye diseases among school children, *Rinsho Ganka (Clin. Ophth.), 14,* 1960, 1762-1769.

2 Waaler, G. H. M., Über die Erblichkeitsverhältnisse der verschiedenen Arten von angeborener Rotgrünblindheit, *Acta ophth., 5,* 1927, 309-345.

3 Planta, P. von, Die Häufigkeit der angeborenen Farbensinnstörungen bei Knaben und Mädchen und ihre Feststellung durch die üblichen klinischen Proben, *Gräfes Arch. Ophth., 120,* 1928, 253-281.

4 Wieland, M., Untersuchungen über Farbenschwäche bei Konduktorinnen, *Gräfes Arch. Ophth., 130,* 1933, 441-462.

5 Trendelenburg, W., and Schmidt, I., 1935. Cited from François, J., *Heredity in Ophthalmology,* Mosby, 1961.

6 Schmidt, I., 1936, Cited from François, J., *Heredity in Ophthalmology,* Mosby, 1961.

7 Nelson, J. H., Anomalous trichromatism and its relation to normal trichromatism, *Phys. Soc., 50,* 1938, 661-702.

8 François, J., *et al.*, 1956, Cited from François, J., *Heredity in Ophthalmology,* Mosby, 1961.

9 Nakajima, A., *et al., op. cit.*

10 Nemoto, H., and Murao, M., A genetic study on color blindness, *Jap. J. Human Gen., 6,* 1961, 165-172.

TABLE II

SEX DISTRIBUTION OF HARELIP AND CLEFT PALATE IN JAPANESE AND CAUCASIANS

		JAPANESE			CAUCASIANS	
		*Maternity wards**	*General hospitals*			
Types		*Japanese Red Cross*[11] *and Hikida*[12]	*Kyushu University*[13]	*Tokyo Med. Dent. Univ.*[14]	*Pennsylvania U.S.A.*[15]	*Denmark*[16]
(1) Harelip	Females	29	578	73	95	48
	Males	30	505	68	197	90
	% Males	50.8	46.6	48.2	67.5	65.2
(2) Harelip +	Females	28	332	95	150	103
Cleft	Males	50	654	195	278	257
Palate	% Males	64.1	66.3	67.2	65.0	71.4
(3) Cleft	Females	21	252	98	106	84
Palate	Males	10	133	52	75	43
	% Males	32.3	34.5	34.7	41.4	33.9
Total	Females	78	1162	267	351	235
	Males	90	1292	317	550	390
	% Males	53.6	52.6	54.3	61.0	62.4

* Includes miscarriages and stillbirths.

in Japanese as in European populations. The ratio of the percentage of deuteranomaly to that of deuteranopia ranges from 2.0 to 4.9 among Caucasians but is less than 1.3 among Japanese (see Table I).

Ethnic differences in the incidence of harelip and cleft palate are much more difficult to interpret. These characters appear to be due to diverse genetic factors, some of which depend for their manifestation on environmental variables.

The over-all incidence of harelip and cleft palate among Japanese is at least 1.5 times more frequent than in Caucasians. If the malformations are classified into three types: (1) harelip without cleft palate, (2) harelip with cleft palate, and (3) cleft palate without harelip, the difference is most striking with respect to female cases of type 1. These are 3.5 times more frequent in Japanese. In Japan, males constitute only 50 percent or less of these cases, whereas among Europeans the sex ratio is much higher. In classes 2 and 3 the sex ratio is fairly similar for both races (see Table II). These racial differences in the sex ratio certainly reflect heterogeneity

11 Mitani, S., Malformations of the newborn infants, *J. Jap. Obst. Gynec, Soc., 1,* 1954, 301-315.

12 Hikida, Z., Incidence of harelip and cleft palate in the city of Nagasaki, *J. Nagasaki Med. Assoc., 28,* 1953, 1371-1375.

13 Sanui, Y., in press.

14 Kobayasi, Y., A genetic study of harelip and cleft palate, *Jap. J. Hum. Gen., 3,* 1958, 73-107.

15 Ivy, R. H., Modern concept of cleft lip and cleft palate management, *Plast. Reconstr. Surg., 9,* 1952, 121.

16 Fogh-Andersen, P., *Inheritance of Harelip and Cleft Palate,* Opera ex Domo Biol. Hered. Hum. Univ. Haf. Vol. 4, Munksgaard, Kopenhagen, 1943.

of causation, but it is impossible to distinguish between environmental and genetic variables. It is almost certain that a series of genes with different modes of inheritance are responsible for these developmental disturbances.

Several authors hold that harelip with or without cleft palate is inherited as an autosomal recessive character whereas cleft palate is an autosomal dominant character. The results of consanguinity studies are at variance with this assumption. An extensive survey on 2400 cases of these abnormalities was carried out in the Department of Oral Surgery of Kyushu University. The rate of consanguineous marriage among parents of cleft-palate patients was significantly higher than that in the general population, pointing to recessive inheritance. Parents of patients with harelip (types 1 and 2) showed no higher consanguinity rate than the general population.

In conclusion, I might mention a very rare abnormality. We Japanese human geneticists occasionally come across cases of shortening of the fourth metatarsal bone. This abnormality begins to manifest itself at early school age and is sometimes combined with shortening of the fourth metacarpal bone. It is sometimes transmitted as an irregular autosomal dominant trait. However, most cases are sporadic.

Most patients are females. We found 3 cases of this abnormality among 3115 schoolgirls examined in Shizuoka.[17] This is an incidence of 0.1 percent, but no case has been found among boys in a sample of similar size. I suspect that this abnormality is very rare among Western people.

FREIRE-MAIA: I would like to call your attention to achiropody, causing abrupt termination of the limbs, above the elbow and below the knee. This syndrome is also referred to as quadruple congenital "amputation." All the cases known thus far have been found in Brazil, in families of Portuguese origin. It is a condition due to an extremely rare autosomal recessive gene subject to strong negative selection, since the affected individuals have a very high perinatal mortality and a very low fertility. This problem has been fully analyzed elsewhere.[1-3]

HIRSCHHORN: Much of the discussion during this meeting has been devoted to population surveys. Now that Dr. Tanaka and Dr. Freire-Maia have turned our attention to the subject of congenital malformations, I should like to make a suggestion as to a type of population study that has not been mentioned thus far, which is one relating to chromosomal anomalies, both major and minor. I am

17 Sugiura, Y., *et al.*, On the skeletal variants in hands and feet of Japanese children, *J. Jap. Orthop. Assoc.*, *35*, 1961, 925-926.

1 Freire-Maia, A., Freire-Maia, N., and Quelce-Salgado, A., Genetic aspects of achiropody, Proceedings, Tenth International Congress of Genetics, Montreal, University of Toronto Press, 1958, pp. 88-89.

2 Freire-Maia, N., Quelce-Salgado, A., and Amundsen-Koehler, R., Hereditary bone aplasias and hypoplasias of the upper extremities, *Acta genet. Stat. Med.*, *9*, 1959, 33-40.

3 Freire-Maia, A., (1961). New data on achiropodia, Proceedings, Second International Conference on Human Genetics, Rome. (In press.)

particularly referring to the minor ones, and this derives from a finding that we have made recently.[1]

On examining a boy with a rather mild congenital anomaly, we discovered that in one of his small acrocentric chromosomes the satellites were markedly enlarged. At first we wondered whether this was related to his disease, but we decided to study his family. We found that the father had these so-called giant satellites whereas the mother did not. These enlarged satellites were present in his oldest and in his youngest sisters, whereas his middle sister did not possess them. Very soon thereafter we found two more families with enlarged satellites on a large acrocentric chromosome and decided to begin a search for an incidence of this factor in the population. Just a few weeks ago, we began going around the wards taking people at random and the third individual whom we picked, a 61-year-old male who was in the hospital with a myocardial infarction and had lived perfectly normally all his life, turned out to have these giant satellites. On closer examination it was found that, in addition to these giant satellites, he also had a translocation between two long acrocentric chromosomes. I think that both for the obvious use of such morphological markers in linkage studies and for the interpretation of the significance of chromosomal anomalies in normal and in diseased individuals, a population study may be advisable. For example, in a child with relatively minor congenital anomalies, we found an apparent deletion of most of the short arm of one chromosome in group 4-5.[2]

STEINBERG: Dr. Hirschhorn has touched upon the subject of chromosomal anomalies, which in these days ranks foremost in the minds of most human geneticists. I am sorry that this debate will have to be adjourned because of the advanced hour, and I wish to thank all the speakers and discussants.

1 Cooper, H. L., and Hirschhorn, K., Enlarged satellites as a familial chromosome marker, *Am. J. Human Gen., 14,* 1962, 107-124.

2 Hirschhorn, K., and Cooper, H. L., Partial deletion of one chromosome 4/5 in a child with congenital anomalies, *Cytogenetics,* 1962. (In press.)

SESSION 4 J. V. NEEL, *Chairman*

GENETIC STUDIES IN ISOLATES

NEEL: We have so full a program this morning that we can dispense with any preliminary remarks from the chairman. The first paper of the morning will be presented by Dr. K. R. Dronamraju of India.

K. R. DRONAMRAJU

Genetic Studies of the Andhra Pradesh Population

Andhra Pradesh is a linguistic territory of southeastern India inhabited by 33 million Telugu-speaking people. The state is not isolated geographically from the neighboring states of India and is bordered by the Bay of Bengal on the eastern side. Most of the population investigated lives in the coastal districts.

CONSANGUINEOUS MARRIAGES

Consanguinity records have been made[1] in the Bombay region on the west coast, but we have no previous quantitative record of consanguinity in the districts of the east coast, though it has been mentioned occasionally in various anthropological books.

The Moslem invasions into this region from the north during the past thousand years resulted in Moslems settling in this part of India. This, however, has not seriously affected the customs of the local people in the region in which our study was conducted. Here the inhabitants are now mostly Hindu, some Christian, and a few Moslem. There are five traditional occupational groups among the Hindus, each of which has its own social customs.[2] These are *Brahmans, Kshatriyas, Vaisyas, Sudras,* and *Harijans* (formerly "untouchables"). These are Sanskrit names which have been in use for many hundreds of years. Each of the first three groups consists of a few subgroups which were traditionally endogamous. The *Sudras,* who have been regarded as one of the lowest social groups, superior only to the *Harijans,* consist of many subgroups, some of which are still largely endogamous. This social system is now changing and the traditionally endogamous groups are beginning to break down and to intermarry. Consanguineous marriages were known to be preferred in this region for many hundreds of years. Since marriages are rarely registered, we have collected information by direct questioning.

The information given in Table I was obtained through two independent sources. First, my colleague, Dr. P. Meera Khan, questioned patients in the King

1 Sanghvi, L. D., Varde, D. S., and Master, H. R., Frequency of consanguineous marriages in twelve endogamous groups in Bombay, *Acta genet., 6,* 1956, 41-49.
2 Dronamraju, K. R., and Meera Khan, P., Inbreeding in Andhra Pradesh, *J. Hered., LI,* 1960, 239-242.

George Hospital, Visakhapatnam, about their own marriages, their parents marriages, and their children's marriages. Most of the patients were accompanied, throughout their stay in the hospital, by a close relative or spouse who frequently helped supply the information. Secondly, we sent questionnaires through school children to their parents inquiring about these parents' marriages. Neither the hospital, which is the largest in the state, or the schools restricts admission to any particular group of people.

TABLE I
CLASSIFICATION OF MARRIAGES

	Parents of		*Patients*	*Children of patients*	*Total*
	School children	*Inpatients*			
Nephew	1	0	0	0	1
Maternal uncle	31	42	65	18	156
Paternal uncle	0	1	0	0	1
Maternal uncle's son	30	24	31	9	94
Paternal aunt's son	51	87	88	40	266
Maternal aunt's son	0	1	1	0	2
Other relationships	13	32	53	48	146
Consanguineous total	126	187	238	115	666
Nonconsanguineous	360	559	367	225	1511
Percentages	25.9	25.9	39.3	33.8	30.5

The most frequent type of consanguineous marriage is between a girl and her paternal aunt's son; 266 marriages of this type are recorded. Uncle-niece marriages are also fairly common. Out of 2177 marriages recorded, 666 are consanguineous. These include such remoter kinds of consanguineous marriages, as between second cousins, second cousins once removed, and third cousins.

TABLE II
COEFFICIENTS OF INBREEDING

	No. of marriages	*F*
Parents of school children	486	.0194
Parents of patients	746	.0175
Patients	605	.0278
Patients' children	340	.0186
All marriages	2177	.0209
Patients with malformations	10	.0250
abortions	55	.0304
pulmonary tuberculosis	38	.0339

The coefficients of inbreeding for all marriages in different groups are given in Table II. The mean coefficient for all marriages is .0209. The value of the coefficient for the parents of patients suffering from pulmonary tuberculosis is significantly higher than that of "controls" at the 5-percent level. For congenital malformations

and abortions, this value is also elevated but not significantly so at the 5-percent level.

Because differences between samples reveal that information about consanguinity remoter than the first-cousin relationship is incomplete, the coefficients of inbreeding were recalculated omitting these more distant relationships. These values are presented in the second column of Table III.

TABLE III
COEFFICIENTS OF INBREEDING

	Based on all consanguineous marriages	*Based on first-cousin marriages and closer relationships*
Parents of school children	.0194	.0187
Parents of patients	.0175	.0167
Patients	.0278	.0260
Patients' children	.0186	.0157
Total	.0209	.0195

TABLE IV
PARENTAL CONSANGUINITY

	MARRIAGES OF PATIENTS' PARENTS						
Diagnosis of patients	*Maternal uncle*	*Maternal uncle's son*	*Maternal aunt's son*	*Paternal aunt's son*	*Other relationships*	*Total*	*Percentage of consanguinity*
Cancer	5	1	0	10	1	68	25.0
Pulmonary T.B.	6	2	0	6	2	38	42.1
Other kinds of T.B.	1	4	0	6	1	39	30.8
Diseases of C.V.S.	1	2	1	7	3	61	23.0
Diseases of C.N.S.	3	2	0	6	2	62	21.0
Resp. diseases	6	3	0	8	4	58	36.2
Deficiency diseases	2	1	4	0	0	35	31.4
Injuries	1	1	0	5	1	40	20.0
Malformations	2	6	0	1	1	24	41.7

The differences between the first and second coefficient are higher for patients' and their children's marriages, because remoter relationships contributed more to the values of F for marriages of patients and their children than to those of parents of patients and school children.

The percentages of consanguineous marriages among the parents of different diagnostic groups of patients are shown in Table IV. None of these percentages, except for pulmonary tuberculosis, is significantly different from the average. Consanguinity is positively correlated with the rural background and illiteracy of the spouses (Table V).

It is clear that the differences in the mean coefficients of inbreeding, or in overall frequencies of consanguinity, between different groups can be due to any of the

four following causes: *(a)* true biological effects of inbreeding; *(b)* correlation of marriage type with hygienic conditions; *(c)* differences in knowledge between different groups; *(d)* "sampling errors"—*i.e.*, chance effects due to the small size of the sample.

There may be other possibilities. For example, it is possible that a physician may inspire more confidence in one group of patients than in another and thus obtain more information from them. The remarkable agreement between the values of F for parents of school children and parents of patients argues against the importance of cause *b*.

TABLE V*

CLASSIFICATION OF PATIENTS' MARRIAGES BASED ON THEIR PLACES OF ORIGIN AND EDUCATION

	Rural illiterate	*Rural literate*	*Urban illiterate*	*Urban literate*	*Totals*
Consanguineous	114	46	41	29	230
Nonconsanguineous	122	57	58	87	324
Totals	236	103	99	116	554

* Some patients, on whom data were unavailable, are not included here.

Because no records of earlier marriages are available, we do not know how much decrease or increase there has been in the values of the coefficient in recent years. We can in future estimate such changes as Dr. Sutter and his colleagues estimated in the departments of France.[3] This would also provide enough data to ascertain the importance of inbreeding in the etiology of various diseases and malformations. The frequency of recessive allelomorphs in a population with a long-established mating system is expected to be close to equilibrium, and the time required to reach this equilibrium in populations will depend on the coefficient of inbreeding. We do not expect to find a high frequency of abnormalities in the Andhra Pradesh population, because many of the deleterious genes must have been eliminated by natural selection in the course of continuous inbreeding at a high rate for many hundreds of years. We hope to know the answer in a few years.

Before discussing the gene frequencies in some of the polymorphic systems studied in this population, I should like to add a few words about the nature of the social isolates in Andhra Pradesh. The different social groups, which are endogamous in the Hindu social system, are no doubt isolates, but most of these are made up of several thousand people. There are also some isolates which are made up of a few hundred people. However, in most of the endogamous groups of this population the cause for the very high rate of inbreeding is not the lack of choice

3 Sutter, J., Recherches sur les effets de la consanguinité chez l'homme, *Biol. Méd.*, *47*, 1958, 563-66.

of partners. Among the Cochin Jews (see p. 352), on the other hand, the choice of partners is limited to a small number of people, and here it may be the restricted size of the isolate that determines the type of marriage contracted.

Blood Groups

Thus far we have data for the ABO system only. The data presented in Table VI were recorded during 1955-1960 at the blood bank of the King George Hospital in Visakhapatnam.[4] The most frequent blood group among the Hindus and Christians is O, whereas among Moslems it is B. The similarity in this respect between the Hindus and Christians is compatible with the historical evidence that the Christians are descendants of converts made among the Hindus. Since their

Table VI
The Frequencies of Phenotypes and Genes of the ABO System in Different Population Groups of Andhra Pradesh

	O	*A*	*B*	*AB*	*Totals*	*p*	*q*	*r*	*D*
Hindus	1526	628	1040	147	3341	.1239	.1974	.6787	+ .0035
Christians	142	62	83	17	304	.1395	.1805	.6800	— .0041
Moslems	58	33	65	8	164	.1350	.2572	.6078	+ .0162
Totals	1726	723	1188	172	3809	.1256	.1985	.6759	+ .0033

settlement the Moslems have made fewer converts and have remained largely endogamous. However, the origin of the Moslems remains uncertain since many Hindus, as well as Moslems in the northern Indian states, have more than 20 percent of the B gene.[5] These populations, unlike those of Andhra Pradesh, have undergone various social turmoils, first by foreign invasions and later by religious riots which must have resulted in gene exchange among various communities.

Color Blindness

I should like to mention also our study of the frequency of color blindness in the Andhra Pradesh population.[6] We tested 564 school children. Out of 292 boys, 7.5 percent were found to be color blind with protanomalous and protanopic conditions much more frequent than in other Indian populations and in Europe. One out of 272 girls was found to be definitely color blind, suffering perhaps from a protanomalous condition, but the sub-classification was not very clear.

Hypertrichosis Pinnae Auris

Hypertrichosis pinnae auris is a phenotype characterized by the presence of long

4 Dronamraju, K. R., Meera Khan, P., and Narayana Murty, V. V., ABO Blood Groups of the Andhras Man. (In press.)

5 Mourant, A. E., Copec, A. C., and Domaniewska-Sobczak, K., *The ABO Blood Groups: Comprehensive Tables and Maps of World Distribution,* Blackwell Scientific Publications, Oxford, 1958.

6 Dronamraju, K. R., and Meera Khan, P., Frequency of colour blindness in Andhra Pradesh school children, *Ann. Human Gen., 25,* 1961, 107-110.

hairs on the helix of the ears. I have recorded the frequencies of this character in West Bengal, Andhra Pradesh, and Ceylon (Table VII).[7,8] I have also recorded the frequencies among a few aboriginal tribes from Central and Eastern India. No affected female has been found in any of these places. The frequency of hypertrichosis is higher in both Bengal and Ceylon than in an intermediate region—*i.e.*,

TABLE VII*

FREQUENCIES OF HAIRY PINNAE IN INDIA AND CEYLON

Place	*Subjects*	*Total*	*No. with hairy pinnae*	*Percentage with hairy pinnae*
INDIA				
Andhra Pradesh	Cotravelers	345	21	6.1
West Bengal	Employees of Indian Statistical Institute	150	24	16.0
CEYLON				
General Hospital, Colombo	Outpatients	124	44	35.5
Coconut Research Institute, Lunuwila	Staff and laborers	109	35	32.1
Coconut Seed Multiplication Farm, Ratmalagara	Staff and laborers	60	26	43.3
Department of Agriculture, Peradeniya	Workshop men	58	23	39.7
Royal Botanic Gardens, Peradeniya	Garden staff	63	25	39.7

* Reprinted from *Nature, 190,* 1961, 653.

Andhra Pradesh. This is compatible with the statement in the Mahawamsa, an ancient Sinhalese chronicle, that Ceylon was colonized from Bengal about 2500 years ago. It is clear that there are significant differences between the frequencies in different populations and that the character can be very useful as an anthropological marker. For a careful observer there is no ambiguity in scoring a person as positive or negative in spite of the extreme variation noticed in the expression of the trait.[9] I would like to add that this is also relevant to the subject of migration and drift in polymorphic systems.

NEEL: Thank you, Dr. Dronamraju, for a most interesting paper. Our next paper will be that of Prof. Sutter, of France.

7 Dronamraju, K. R., Hypertrichosis of the pinna of the human ear. Y-linked pedigrees, *J. Gen., 57,* 1960, 230-244.

8 Dronamraju, K. R., Frequencies of hairy pinnae among Indian and Sinhalese peoples, *Nature, 190,* 1961, 653.

9 Dronamraju, K. R., Hypertrichosis of the pinna of the human ear. Y-linked pedigrees, *J. Gen., 57,* 1960, 230-244.

J. SUTTER

The Relationship Between Human Population Genetics and Demography

I

With the development of human genetics the choice of populations to be studied, or the choice of the groups within such populations, assumes an increasing importance. Unfortunately, the field of studies is as a rule defined in much too general terms. It might even be said that this aspect of research is frequently neglected. Blood-group experts are undoubtedly most directly responsible for this regrettable situation. Since one applies Fisher's formulas on the assumption that the blood groups are independent of age and sex, there is a tendency to confine research to any random sample of the population, which is only rarely representative of its real demographic structure. Even the disputable assumption that this approach, which is objectionable from the demographic point of view, will only rarely affect the value of the observations on blood-group frequencies hardly applies to most other spheres of genetic research.

Unfortunately the students of population genetics tend all too often to adopt the methods of the blood-group experts. This procedure is questionable not only from the demographic point of view but from the genetic aspect as well. The essential feature of the problem—namely, the influence of gene frequencies—is thus neglected. Whereas the choice of the group to be studied may be of little importance in the investigation of widely distributed characters such as the ABO blood groups, for which any individual must possess two of the genes concerned, this is no longer true if the gene in question exists in only a few individuals—in other words, if its frequency is 0.1 percent or less.

This is usually the case in medical genetic research, and here the sampling of the group to be studied assumes major importance. As early as 1911, S. M. Jacob[1] showed that the risk involved in consanguineous marriages derives precisely from the fact that the rarer a recessive gene, the higher will be the chance of encountering the affected homozygotes among the offspring of consanguineous marriages. Also, the higher the frequency of cousin marriages in the population, the larger will be their contribution to the total of affected homozygotes. Under these conditions, the method of sampling employed in estimating the frequencies of carriers as well as of genes and gametes within a population assumes paramount importance.

The effect of the frequency of carriers is one of the points that has been most

1 Jacob, S. M., Inbreeding in a stable Mendelian population with special reference to cousin marriage, *Proc. Roy. Soc. London*, S.B. *84*, 1911, 23–42.

misunderstood by human population geneticists. Certain widely read and highly influential works may be cited which show a completely erroneous orientation on this point.

II

It is a curious fact that the recent progress in consanguinity studies and the numerous investigations carried out during the past few years on isolates or small population groups have failed to alter the concept of investigators in this field. It is illogical to work on numerically limited populations with the aid of models constructed by mathematicians visualizing an infinite population in the mathematical sense. More specifically, it should be noted that all the formulas applied to the study of smaller groups are based on the assumption of panmixis, whereas it is well known that panmixis cannot occur in human populations, especially if they are limited in numbers. This constitutes a source of grave contradictions and is bound to blur our realistic vision of problems and facts.

Six arguments may be raised against the strict application of the concept of panmixis to human populations: (1) differential fertility, resulting in different family sizes for different couples: (2) migrations; (3) assortative mating; (4) mutations; (5) preference for consanguineous marriages; and (6) population size. By far the most important among these factors is differential fertility. We speak of genetic drift and selection, frequently ignoring the fact that the object of our observations is controlled by demographic factors that can be interpreted at only two levels: fertility and mortality.

It might be argued that geneticists are solely concerned with fertility. They want to determine for any given couple the number of offspring reaching the age of reproduction. The essence of all the partial hypotheses constituting the idea of panmixis is most distinctly reflected in the fertility of couples. One might therefore assume that the measurement of fertility should play a major role in population genetics. This, however, is far from being the case. This conference, devoted to the genetics of human populations, offers a welcome opportunity to discuss the potential contribution of demography to the accurate measurement of fertility.

The importance of differential fertility in populations may well be demonstrated by a computation of Pearson relating to Denmark. In 1830, 50 percent of the children in that country had issued from 25 percent of the parents. In the same trend of fertility, 73 percent of the Danes at the second generation and 97 percent at the third were the descendants of the early 25 percent. Before World War I, Davenport, taking account of differential fertility, made the following computation: 1000 Harvard graduates would have only 50 descendants after two centuries, whereas 1000 Romanian immigrants living in Boston would have multiplied to 100,000. In France we have recently made a computation showing that by the same mechanism only 12 percent of the Frenchmen living at the moment of the Great Revolution (1789) were represented by their progeny in the generation living in 1880. Such changes indicate the importance of fertility factors in genetic studies.

III

Let us now examine the demographic data. The reproduction of the human species depends on fecundity and fertility, which may be estimated for men, women, or couples. Few scientists in the field of genetics took these points seriously into account in the construction of the models or in more practical studies. It is only in the works of Prof. J. B. S. Haldane that this aspect is stressed, particularly in his studies on the genetic mechanism of evolution. At least his considerations are near to those of Lotka,[2] the father of the measure of fertility in demography.

Crude Birth Rate

The crude birth rate is the ratio of live births per calendar year to the average population of the same year expressed in thousands. For instance, its value, in 1957, was 16.4 for the United Kingdom and 49.5 for Ruanda-Urundi in Africa. By the way, its value in Europe before the wide spread of birth control was between 35 and 40. In underdeveloped areas it is still between 40 and 50.

The crude rate is rarely a useful measure in genetic studies. The durations of the reproductive period are too diverse. The nuptiality—*i.e.*, the frequency of marriages—is too variable among populations, and birth control has not been practiced to the same extent in different groups.

The General Fertility Rate

The general fertility rate is the ratio of the live births per year to the average number of women of reproductive age—*i.e.*, between 15 and 49. This rate is useful only when the age distributions in the populations are very dissimilar. In practice the result differs very little from the crude birth rate.

The Rates by Age Groups

The rates by age groups indicate the fertility according to the age reached by the mother during a given year.

Demographic experience shows that these rates may differ widely, depending on whether the populations are Malthusian—*i.e.*, limit the number of births—or not.

If we are dealing with a natural population with unlimited fertility, grouping by age of mothers is sufficient because the age at marriage does not seem to affect the fertility of women of a given age. If we are dealing with a Malthusian population, the rates by age groups assume great interest, especially if computed by age of mothers and by their age at marriage.

No ideal technique has been devised as yet for the Malthusian populations. Yet it is better to take into account the woman's age at marriage than her age at the birth of a given child. We shall return later to this basic fact.

2 Lotka, A. J., *Théorie Analytique des Associations Biologiques.* IIme Partie. Analyse démographique avec application particulière à l'espèce humaine, Act. Sc. & Ind. No. 780, 1939.

Computation of Fertility Rates from Family Histories

To compute fertility rates from family histories, we reconstruct the families from the archives—for example, from parish registrations such as utilized by Dr. Cavalli-Sforza in his study (see p. 34) or from systematic family registrations known as Koseki or Honseki in Japan. In this case the fertility rate for the age group 25-29, for example, may be obtained by dividing the number of births in this group by the number of years lived in wedlock between the 25th and 30th birthdays for all the women studied. A rigorous count in "woman-year" units must be done. This count of "woman-years" is important in the study of historial problems in genetics.

Having defined the rates of fertility, we proceed to examine the rates of reproduction. Here we are getting nearer to the aims of genetics, since these rates concern more directly the mechanism by which one generation replaces another.

Crude Rates of Reproduction

From a series of fertility rates established by age or groups of ages, we derive for a given group of women the mean number of their female offspring that would be represented in the next generation if there was no mortality. This rate can be established for any age group. We can also determine the crude rate of reproduction of an actual generation by computing the average number of daughters born alive to women surviving at 50. This rate is also better for the non-Malthusian populations than for the Malthusian. Again, to get more accurate results, it is necessary to take the duration of marriage into account. In Malthusian populations, obviously, fertility tends to become zero when the family reaches the desired size. Here fertility is more highly correlated with the duration of marriage than with the age of the wife.

The geneticist's orientation tends to be dynamic and therefore longitudinal. He wants to know what happens from one generation to the next. In recent years the demographic analysis of fertility based on the considerations just outlined has made much progress. The population geneticist is therefore able to choose with more assurance the population to be studied. This method is referred to as "analysis by cohorts" by the American school (P. K. Whelpton[3]), whereas the French (L. Henry[4]) speak of "analysis by promotions."

A cohort or promotion comprises all women born during a 12-month period. To estimate the fertility or mortality, one assumes that these women are all born at the same moment on January 1 of the year.

This method has resulted in the construction of fertility tables which are extremely useful for the estimation of fertility in a human population. As pointed out already, it is advisable to select the cohort to be studied by age at marriage

3 Whelpton, P. K., *Cohort Fertility,* Native White Women in the United States. Princeton Univ. Press, XXV, 1954.

4 Henry, L., *Fécondité des mariages.* Nouvelle méthode de mesure, Paris, I.N.E.D., P.U.F., 1953.

rather than by year of birth. Such a fertility table shows, for each cohort, the cumulative birth rate and the rate for each birth rank according to age of mothers for all women surviving at each age from 16 to 47. For example, the 1900 cohort, at age 20—the women surviving on January 1, 1920—had had 244 births per thousand. (The material is the white woman of the United States.) At 20, the rate for the first-born is 184, for the second 48, for the third 10, for the fourth 2. In 1940, among those surviving at 40 of the 1900 cohort, there are 2537 cumulative births per 1000; 771 for the first child, 602 for the second, 406 for the third, and so on. Certainly if genetic surveys were limited in time to a cohort such as this one, a very dynamic impulse would be given to the studies.

To complete the picture, the work of demographers concerning the probability of family growth should be cited.[5] It appears that this new field of research, which has proved of great importance, may easily be integrated with the models of population genetics. For all the reasons indicated, the estimation of gene frequencies and of other statistics in human populations encounters numerous difficulties so long as the demographic structure or the reproductive characteristics of the populations are not taken into account.

IV

A rapid examination of these different rates shows that the "crude birth rate" and the "general rate of fertility" have not much bearing on the dynamic aspects of genetic research. The "rates by age groups" are of greater interest. It is conceivable to study two sections of a given population on the basis of demographic data. Thus, when studying first the 50-to-60-year age group and next the 20-to-30-year age group, one may define within the second group a fraction who are descendants of the first, since in certain countries demographic statistics may provide series of individuals classified according to the age of the mother at their births. This constitutes the only proper use of age grouping in kinetic research.

If age groups are used without such preliminary delimitations, various demographic factors may interfere with the correct estimation of gene frequencies. Thus bachelors and sterile couples, whose number is often far from negligible, constitute a "dead weight" which may mar the value of such estimates.

In 1954 Bentley Glass[6] suggested that blood-group research should no longer be carried out at random but according to age groups. Still, the aim of this procedure must be constantly borne in mind, since without attention to demographic factors the data cannot be dynamically correlated. The age group of 20 to 25 years will reflect the gene frequency at a given moment. A corresponding study carried out 15 or 20 years later on the same age group will give a new series of data which

5 *Ibid.*

6 Glass, B., Genetic changes in human populations, especially those due to gene flow and genetic drift, *Adv. Gen.*, *6*, 1954, 95-139.

may or may not differ from the first. But if any differences should emerge, one could merely state the fact without being able to explain it. The picture remains static. Of course the findings may be of intrinsic interest, but if the differential fertility is disregarded, the dynamic aspect of the problem is ignored. The demographic mechanism of the phenomenon cannot be grasped and hence many interesting genetic aspects are missed.

An examination of the "rates of reproduction" is even more instructive for the geneticist. Working as described at the age-group level and using demographic statistics involve a laborious effort to construct cohorts of some sort which may be found all ready in "the rate of reproduction." By using the method of cohorts one concentrates on the sector of the population that is of genetic interest. Starting with a group of women well defined in the age pyramid, one may follow their descendants through one or more generations, if necessary, and arrive at a dynamic interpretation of the data.

One may also start out simultaneously with a number of cohorts and then carry out the same research on a group of more recent cohorts, defining the contribution of the first series to the second. In this way a degree of accuracy is achieved which would not have been possible with the method of age groups even under the best conditions.

It may be claimed that in a large modern population it is difficult to use cohorts. This is true. It is much easier to apply this method in smaller countries. It is certainly impossible to utilize it for the large total populations of the United States or France, but it is perfectly well applicable to the Scandinavian countries, such as Sweden or Denmark. In Israel it should present no difficulties. The same applies to the official registration of census of hereditary traits (syndromes) in a given population. It is impossible to envisage an efficient census of genetic diseases in the United States or Great Britain, but a correct census of hemophiliacs and achondroplastics in Denmark and of hemophiliacs in Sweden has been achieved.

The use of cohorts raises another interesting problem—namely, the evaluation of data of the Official Registrar in genetic studies. The United Nations Scientific Committee on the Effects of Atomic Radiation convened an international seminar for the study of this problem at Geneva (September 5-9, 1960) under the auspices of O.M.S.[7] The participants unanimously voiced a plea for a change in the official registration systems, introducing a longitudinal orientation which would permit the utilization of the data in genetic research. On that occasion we stressed the need for the application of the cohort method. Hitherto, however, only a single country, Canada, has invested enormous efforts for several years in order to facilitate the longitudinal use of demographic data. An experiment in this direction extending over an entire province of Canada is at present being carried out by the promoter of this plan (Newcombe). With the system of demographic registration envisaged

7 *Seminar on Use of Vital and Health Statistics for Genetic and Radiation Studies*, O.N.U. Genève, 1960.

by him it will become easy for geneticists to carry out the calculations outlined above for individual cohorts.

V

Although the study by cohorts is by far the most attractive and satisfactory method, it should be realized that genealogies will still provide the safest basis for genetic studies. Special interest may be derived from working on a population whose genealogy has been established in advance. First, the transmission of a character from one generation to the next, its dominance, recessivity, penetrance, and expressivity may be studied by direct inspection of pedigrees. Moreover, any fertility differential due to this character will emerge from longitudinal analysis between generations, age groups, or by the cohort method. Cohorts or, more simply, families may be followed over a period of time while the demographic and genetic evolution of the population is simultaneously investigated. In certain cases it may even be of interest, when using the cohort method, to concentrate on women only in order to study the evolution of a certain characteristic during successive generations. Such a systematic investigation can also be carried out on only a single group comprising three or four living generations.

Hitherto the genealogical method was applicable only to populations of a limited size. The recent progress in mechanical registration and computer technique allows us to envisage its application to the kinetics of much larger populations.

Basically the static aspect of genetics is of little interest to any of us. It is certainly important to know at a given moment the distribution of a certain characteristic within the population. Such data obviously enable valid comparisons to be made between one population and another. Our main preoccupation, however, lies elsewhere. We may aim to investigate the establishment of a common characteristic in a population in order to assess whether its concentration is due to high mutation rate. We must avoid at all costs the "dilution" of the material that is of genetic interest. We are interested, metaphorically speaking, in the events inside a piece of sugar, in observing the behavior of its molecules over the longest period possible. How can this be done if we drop and lose it in a glass of water? We are all preoccupied with Darwinian or pre-Darwinian hypotheses. How can the effect of selection or genetic drift be evaluated if we have only one generation or one group of measurements at our disposal?

The advantages of the genealogical method may be illustrated by an example of its application in the field of anthropology. The Eskimos constituting the Angmagssalik isolate on the east coast of Greenland (about 850 persons) were all measured by Gessain in 1934 and by Skeller in 1950. The anthropometric characteristics of the face appeared to have undergone changes during the intervening period. The classical anthropologists spoke of a "meristic variation"—the disappearance of the seal diminished the need for mastication and this resulted in the

reduction of the jaws. A demographic examination of the genealogy of this group[8] shows, however, that the fertility differential was such that the two populations examined were bound to differ in many respects. Thus, one man who had been married three times was responsible for the fact that over a hundred persons in the isolate of 1950 were first cousins, connected to him as a common ancestor. This fact by itself may give rise to pronounced genetic drift.

Much more might be said about the common interests of population genetics and demography. Yet one of the most important points is still the application of proper sampling techniques in a demographic environment when carrying out genetic research at the population level.[9] The application of the mathematical theory of sampling to the field of demography is still in its infancy, owing to the very complex overlapping of generations. Additional difficulties arise from the differences in family size dependent in part on differences in the age of the couples.

It may be expected, however, that in the future population genetics will proceed to sampling the cohorts and their descendants. No doubt the groups which are the object of genetic study will change their aspect during the years to come. For all the reasons presented here research will be concentrated increasingly at the demographic level, which is its appropriate sphere. Blood-group studies, for example, probably may be confined to a single sex once the ground has been prepared by the cohort method. Similarly the fate of the carriers of rare mutations may be followed up within different cohorts.

An all-out effort is required in order to integrate without delay the techniques of demography with those of population genetics. We are all aware that the progress of our young science requires the establishment of frequencies with a minimum of error. The frequencies of mutations, malformations, genes, and gametes will have to be determined as accurately as possible. The method outlined is the only possible approach to this aim.

NEEL: Thank you, Dr. Sutter. Dr. Roberts wishes to support your plea for closer cooperation between geneticists and demographers.

ROBERTS: Mr. Chairman, I just want to comment on a few points arising from Dr. Sutter's remarks but, before doing so, may I remark, by way of an aside, that I am a little perturbed at the various uses of the word "isolate" that are being employed this morning. It seems that we are applying the same term in a number of different situations, and I hope that confusion may be avoided by agreement on restriction of usage.

The first point of Dr. Sutter's that I want to take up is his remark that the net reproduction rate based on the offspring of females may constitute a useful measure

8 Sutter, J., and Tabah, L., Méthode mécanographique pour établir la généalogie d'une population. Application à l'étude des esquimaux polaires, *Population, 11,* 1956, 507-530.
9 Pressat, R., *L'Analyse démographique. Méthodes—Résultats—Applications,* I.N.E.D., P.U.F., XII, 1961.

in demographic work. Indeed it is, but in the 1930's a number of predictions of future population growth were made on the apparently biological basis of the net reproduction rate calculated for females. Comparison of the predictions with the subsequent growth of these populations has shown that the net reproduction rate based on males exerts a far greater influence on population growth than was thought in the 1930's. For this reason, I would like to draw your attention to another useful biological parameter that has been developed over the past few years—namely, the probability of increase of family size.

Next, I want to stress the importance of closer contact between scientists working on population numbers from the census point of view and those who are applying them in genetic studies. All too frequently we find that data on particular populations in whose genetics we are interested are just not available, largely because the census people have been interested primarily in data for administrative and not for biological purposes. I understand that in Israel all persons who are born here are classified together without further specifications, whereas I should hope that it may be possible to obtain more informative data detailed by parentage.

Finally, I want to emphasize the importance of this contribution from Dr. Sutter on the Eskimo group. For several years now there has been considerable argument as to whether drift occurs in human populations. A number of us have been looking at the demographic material in order to calculate whether the demographic structure of populations could lead to appreciable drift. Drift occurs primarily, as you know, by the random sampling effects involved in the reproductive process. Another extremely important instance in which it occurs, to which Sewall Wright drew attention long ago, is the population "bottleneck," or the period of extreme dwindling in population size. Now, Dr. Sutter's analysis presented this morning shows for the first time that such bottlenecks do occur in small human populations not as a result of tragedies and catastrophes—drownings, epidemics, and so forth—but normally, as result of differential fertility.

NEEL: Before you sit down, a number of members of the audience request that you give your definition of an isolate.

ROBERTS: When this august gathering has failed to reach agreement, Mr. Chairman, I hesitate. [*Laughter.*] I suggest that we consider restricting the isolate concept to those breeding entities within a culturally homogeneous population which by their existence promote genetic heterogeneity among one another and homogeneity within themselves. They thus may give rise to otherwise inexplicable local genotype frequency variations within a population.

Such a definition would distinguish them (*a*) from those small isolated populations in which the breeding unit embraces the population as a whole—*e.g.*, the Pitcairn Islanders; and (*b*) from the relatively large segments, distinct socially or in other ways, of a geographic population—*e.g.*, castes, within which isolates as defined exist. In both of these, gene frequency variation is not inexplicable.

NEEL: Thank you, Dr. Roberts. Our next spaeker this morning is Prof. Tanaka from Japan.

KATUMI TANAKA

Consanguinity Study on Japanese Populations

The Japanese people may be considered, in several respects, as favorable material for consanguinity studies and other genetic investigations. First, consanguineous marriages are much more common in Japan than in most Western countries. Moreover, families are larger and their members are less dispersed, and family registration is complete and reliable. Through these records, blood relationship between any individuals is easily traceable. The Japanese population, comprising nearly 100 million people, is fairly homogeneous in its genetic constitution. Ninety-nine percent of the children go to school for at least nine years. A sample of Japanese school children is thus fairly representative of the population as a whole and not of any particular group or social stratum.

In November 1957, the Science Council of Japan appointed a "Subcommittee" for Consanguinity Study to be affiliated with the "Genetics Committee." This Subcommittee, under the chairmanship of Dr. T. Komai, secured the cooperation of 64 investigators and many collaborators. A research project was outlined and activities were started in the summer of 1958 with the support of the Ministry of Education of the Japanese Government and the Rockefeller Foundation.

Our activities are concentrated on three major studies: (1) on school children in Shizuoka; (2) on residents of isolated villages; and (3) on patients suffering from certain hereditary diseases. In all three projects most of the field work is now completed, and we are in the stage of arranging the data for statistical treatment and genetic analyses. This presentation is thus merely an interim report.

The Shizuoka Studies

The city of Shizuoka, located near the center of Japan, has about 300,000 inhabitants.* The pupils of twelve primary schools of the city, comprising 9320 children aged 6 to 12 years, were subjected to anthropometric and psychometric measurements and to medical examinations. Great efforts were made to obtain accurate data on any blood relationship existing between the parents of these children. The family registration records in the city office as well as in administrative offices of other cities, towns, and villages were carefully searched. It was often possible to trace pedigrees as far as five generations back. The consanguinity data thus obtained were carefully cross-checked by interviewing the parents

* The Japanese definition of a city is somewhat different from that accepted in Europe and the U.S. A city may embrace an extensive geographic area, and the suburbs actually in this instance are relatively small agricultural or fishing villages in the immediate vicinity of Shizuoka, which for administrative purposes are regarded as a part of the city.

TABLE I

GROUPING OF SHIZUOKA SCHOOLS

Sample	*Location*	*No. of schools*	*No. of families*	*Range of average F of school population*
A	peripheral	4	823	0.00749 - 0.01157
B	intermediate	6	3142	0.00412 - 0.00667
C	central	2	2195	0.00236 - 0.00246

and other relatives of the children. This genealogical work also yielded data on the mortality in the sibships including our propositi.

The rate of first-cousin marriages among the parents of the propositi was 4.42 percent and the mean coefficient of inbreeding (F) of the children was 0.0044. This coefficient was higher (0.00822) among residents of the suburban regions than in the center of the city (0.00238). In fact, the coefficient of inbreeding for the pupils of the twelve schools varied fairly regularly according to the central or peripheral location of the school. The schools were therefore divided into three subgroups according to their location, as indicated in Table I.

TABLE II

MORTALITY FROM BIRTH TO SIXTH YEAR

			No. of live births	*Deaths within 7 days*		*Deaths within 8-30 days*		*Deaths within 1-12 months*		*Deaths in childhood (1-6 years)*		*Total*	
				No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Group A.	1.	F = 1/16 or greater	276	8	2.90	2	0.72	9	3.26	13	4.71	32	11.59
	2.	F = 0	768	15	1.95	16	2.08	27	3.52	32	4.17	90	11.72
		difference			0.95		—1.36		—0.26		0.54		—0.13
Group B	1.	F = 1/16 or greater	627	12	1.91	10	1.60	30	4.79	32	5.10	84	13.40
	2.	F = 0	2112	33	1.56	22	1.04	76	3.60	72	3.41	203	9.61
		difference			0.35		0.56		1.19		1.69		3.79*
Group C	1.	F = 1/16 or greater	217	4	1.84	8	3.69	6	2.77	11	5.07	29	13.36
	2.	F = 0	6746	112	1.66	64	0.95	185	2.74	217	3.22	578	8.57
		difference			0.18		2.74		0.03		1.85		4.79†
Total	1.	F = 1/16 or greater	1120	24	2.14	20	1.79	45	4.02	56	5.00	145	12.95
	2.	F = 0	9626	160	1.66	102	1.06	288	2.99	321	3.33	871	9.05
		difference			0.48		0.73		1.03		1.67		3.90
Rate of increase of death rate‡					0.29		0.69		0.34		0.50		0.43

* $p < 0.01$.

† $p < 0.05$.

‡ Calculated as follows: $\frac{\text{Death rate in consanguineous group} - \text{death rate in nonconsanguineous group}}{\text{death rate in nonconsanguineous group}}$

The mortality rates from birth to age of 6 in consanguineous and nonconsanguineous families of the three groups are shown in Table II. Mortality in families of unrelated parents is higher in the suburban area (group A) than in the other regions (groups B and C), but only in these latter two regions is the mortality among the cousin children significantly higher than among the offspring of unrelated parents. This difference seems to disappear in group A.

We suspect that the poor environmental conditions in the homes of group A have raised the over-all child mortality, thus obscuring the mortality due to inbreeding effects. The difference in mortality between the inbred and the noninbred groups shows no definite trend related to the progress of postnatal development.

In addition to medical examinations and psychometric tests according to Binet-Tanaka, each child was subjected to nine different anthropometric measurements. Dr. K. Ohkura and his assistants arranged all these anthropometric, psychometric, and medical data for statistical treatment, and Dr. K. Ito carried out the mathematical analysis of the data.

These analyses are still in progress and thus far only the data on stature and body weight in groups A and B are available. They appear in Table III. It can be seen that stature and body weight in males of group A and stature in females of group B show significant inbreeding depression, but other regressions are nonsignificant, and body weight in females of group A shows an *increase* with rising inbreeding coefficient. Our data thus appear to indicate that inbreeding depression in stature and body weight, if it exists at all, can be only slight. The recent increase in human body dimensions may therefore not be attributable, in the main, to the breakdown of the isolates.

Studies on Residents of Isolated Villages

Five research teams were recruited from the staff of the local medical schools of Kyushu, Kyoto, Wakayama, Nagano, and Fukushima, and each group concentrated on the study of isolated village populations in the vicinity. It was planned to investigate the breeding structure of the populations and its changing trend, the effect of genetic drift, and the distribution of genes determining various hereditary traits. Also, it was expected that cases of some rare genetic diseases might be discovered in this survey. The data on consanguinity were obtained from family registrations and temple records and by interviewing the resident couples and their relatives. Special attention was paid to fecundity and to mortality, including abortions, stillbirths, and neonatal and infantile deaths.

Dr. T. Yanase is engaged in a comparative study of all the data obtained from these areas. The mean degree of inbreeding is several times higher than in Hiroshima, Nagasaki, and the central region of Shizuoka City. Extremely high average inbreeding coefficients have been observed in several small populations—

TABLE III

REGRESSION OF STATURE AND BODY WEIGHT ON INBREEDING COEFFICIENT AND AGE
(SHIZUOKA SCHOOLS—GROUPS A AND B)

Group	*Sex*	*Sample size*	*Regression equation*	*Bivariate analysis of variance*	*Univariate analysis of variance*	
A	Male	279	$z_1 = 78.2 - 0.188x + 0.419y$	$\begin{bmatrix} -0.188 \\ -0.0570 \end{bmatrix}$*	−0.188†	+0.419†
			$z_2 = 2.19 - 0.057x + 0.195y$		−0.0570‡	+0.195
A	Female	257	$z_1 = 74.2 + 0.0805x + 0.451y$	$\begin{bmatrix} +0.0805 \\ +0.161 \end{bmatrix}$†	+0.0805	+0.451†
			$z_2 = -0.909 + 0.161x + 0.220y$		+0.161†	+0.220†
B	Male	533	$z_1 = 79.7 + 0.0158x + 0.411y$	$\begin{bmatrix} +0.0158 \\ +0.0362 \end{bmatrix}$	+0.0158	+0.411†
			$z_2 = 2.19 + 0.0362x + 0.197y$		+0.0362	+0.197†
B	Female	548	$z_1 = 77.0 - 0.180x + 0.442y$	$\begin{bmatrix} -0.180 \\ -0.0427 \end{bmatrix}$‡	−0.180†	+0.442†
			$z_2 = -0.538 - 0.0427x + 0.227y$		−0.0427	+0.227†

Symbols:
x = numerator of inbreeding coefficient with 128 as denominator.
y = age in months.
z_1 = estimated stature in cm.
z_2 = estimated body weight in kg.
* $p < 0.10$
† $p < 0.01$
‡ $p < 0.05$

e.g., 0.024 in Hosojima and 0.02 in a subgroup in Shiiba. It must be remembered that even such high estimates probably indicate only the lowest limit of the real inbreeding coefficient, since inbreeding must have been practiced for many previous generations. One of the peculiar features of these isolated populations is the fact that double cousin marriages and single cousin marriages several times removed are so frequent that they constitute about 28 and 18 percent, respectively, of the total consanguineous unions. The complex structure of the pedigrees often results in values of F falling between the standard fractions of 1/16, 1/32, and 1/64 (Table IV). Sibships with extremely high inbreeding coefficients such as 3/32 to 3/16 are likewise not rare. It is therefore more accurate to express the degree of inbreeding of an isolated population by the mean and the distribution of the inbreeding coefficient than by rates of first-cousin marriages, first cousins once removed, and second cousins. This applies also to regions A and B of Shizuoka.

The time trend in the degree of isolation was analyzed by grouping the couples according to the decade in which they were married (starting with the class

1906-1915). The consanguinity rate in some of the isolates exhibits a peak around 1916-1935 and thereafter decreases gradually until 1955, when it drops abruptly. This is undoubtedly due to the rising tendency to *matrimonial migration.*

However, the decline in consanguinity rate is neither equal or universal throughout Japan. As pointed out previously by Yanase[1] and others, in isolates with extremely high consanguinity rates such as Hosojima,[2] as well as in large

TABLE IV

DEGREE OF INBREEDING AMONG 1052 SIBSHIPS IN AN ISOLATED POPULATION. SELECTED AT RANDOM FROM THE PRESENT GENERATION

Rate of total consanguinity: 27.186 percent
Mean coefficient of inbreeding: 0.01377

Coefficient of inbreeding	*No. of marriages*	*Percent*
0	766	72.814
0.003906	6	0.570
0.007812	9	0.856
0.011787	1	0.095
0.015626 (= 1/64)	33	3.137
0.019531 — 0.023437	14	1.331
0.031250 (= 1/32)	48	4.563
0.035156 — 0.059570	12	1.141
0.062500 (= 1/16)	121	11.502
0.066406 — 0.109375	39	3.707
0.125000 (= 1/8)	2	0.190
0.187500	1	0.095
Total	1,052	100.001

open populations with low consanguinity rates such as Hiroshima and Nagasaki,[3] the decrease of consanguineous marriages is slight or not recognizable. This situation gives rise to difficulties in the estimation of gene frequencies by methods based on the rates of consanguineous marriages.

In the isolated villages analyzed in this project, all individuals must share numerous common ancestors and the problem of the "extent of consanguinity" as discussed by Stern[4] becomes especially pertinent. Kimura[5] and Yanase[6] proposed

1 Yanase, T., The study of isolated populations with special reference to methodology. I. Breeding structure, *Jap. J. Human Gen., 5,* 1960, 25-45.
2 Ishikuni, N., Nemoto, H., Neel, J. V., Drew, A. L., Yanase, T., and Matsumoto, Y. S., Hosojima, *Am. J. Human Gen., 12,* 1960, 67-75.
3 Neel, J. V., Kodani, M., Brewer, R., and Anderson, R. C., The incidence of consanguineous matings in Japan with remarks on the estimation of comparative gene frequencies and the expected rate of appearance of induced recessive mutations, *Am. J. Human Gen., 1,* 1949, 156-178.
4 Stern, C., *Principles of Human Genetics,* Freeman, San Francisco, 1960, pp. 370-371.
5 Kimura, M., Personal communication to Dr. Yanase, 1960.
6 Yanase, T., The study of isolated populations. II. An estimation of endogamy (E), *Jap. J. Human Gen., 7,* 1962. (In press.)

to calculate the real F value by adding the value of E (additional coefficient of inbreeding) to the observed value of F. This mode of calculation has been applied to some isolates in Kyushu by Yanase.[7]

It is generally realized that the inbreeding coefficient for sex-linked genes (F′) differs according to the subtypes of consanguineous marriages. Whereas F′ is zero for the marriage of the children of two brothers (D) and for the union of brother's son with sister's daughter (C), it amounts to 1/8 for the mating of sister's son with brother's daughter (B) and rises to 3/16 for the mating of the offspring of two sisters (A).

TABLE V

INCIDENCE OF SUBTYPES OF CONSANGUINEOUS MATINGS IN THREE ISOLATED POPULATIONS

	*Number of first-cousin marriages of types:**					
Population	A	B	C	D	*Total*	*Mean of F′*
Oshima	13	19	21	13	66	.07292
Hoshino	53	77	47	65	242	.08084
Onodani	15	17	18	19	69	.07156

* See text for explanation of types A through D.

Cousin unions of types A and B are the more common in European populations[8-10] and in Hiroshima, Nagasaki, and Kure, whereas all four subtypes occur with rather equal frequencies in three isolated populations of Japan—Oshima, Hoshino, and Onodani (Table V).

STUDIES OF PATIENTS SUFFERING FROM CERTAIN HEREDITARY DISEASES

It is well known that, in the study of recessive disorders, consanguinity data are particularly valuable. I shall briefly report the results of an extensive survey on blindness carried out by Nakajima in collaboration with Hagiwara.[11] He made a nationwide study of the causes of blindness in inmates of schools for the blind and in rehabilitation centers. In response to the questionnaires sent out to these institutions, he obtained information on 8709 blind persons. Of these patients, 23.3 percent were the children of consanguineous marriages, including 16.7 percent from first-cousin marriages. The analysis of the material thus obtained enabled him to re-examine the current views on the inheritance of some eye diseases (Table VI). For each pathological entity listed in the table, the consanguinity rate is higher among parents of familial cases than among parents of sporadic

7 *Ibid.*
8 Stern, C., *loc. cit.*
9 Kimura, M., *loc. cit.*
10 Yanase, T., The study of isolated populations. II. An estimation of endogamy (E), *Jap. J. Human Gen.*, *7*, 1962. (In press.)
11 Orel, H., Die Verwandtenehen in der Erzdiozöse Wien, *Arch. Rassenk.*, *26*, 1932, 249-278.

TABLE VI
RATE OF FIRST-COUSIN MARRIAGES AMONG PARENTS OF BLIND SCHOOL CHILDREN

	FAMILIAL CASES*		SPORADIC CASES	
	No. cases	*Percent first cousins among parents*	*No. cases*	*Percent first cousins among parents*
Congenital cataract	235	35.7	511	17.2
Microphthalmos	116	20.8	599	8.9
Retinitis pigmentosa	138	44.9	180	32.8
Congenital optic atrophy	111	32.4	245	14.6
Congenital chorioretinal degeneration	49	53.1	93	22.6
Congenital nystagmus	33	50.0	65	38.4
Amblyopia	93	46.2	157	22.9
Buphthalmos	82	37.8	89	12.3
Congenital corneal opacity	88	34.1	356	13.7
Congenital phthisis	63	38.1	338	9.4

* Parents are normal, but some other relatives are affected.

cases. These figures indicate that the familial cases are more often due to recessive genes than the sporadic ones and thus point to a heterogeneous etiology for each one of these defects.

Table VII deals more extensively with one of the defects listed in Table VI—namely, congenital cataract—including patients with one or two affected parents. Although the proportion of first cousins among all parents is 18.08 percent, which is nearly three times the proportion in the general population, this does not apply to the families in which one or both parents were affected. Here the consanguinity rate is similar to that in the general population, making a dominant mode of inheritance very probable.

In families in which the parents are normal but sibs of the propositi are affected,

TABLE VII
RATE OF CONSANGUINEOUS MARRIAGES AMONG PARENTS OF PATIENTS AFFECTED BY CONGENITAL CATARACT (AFTER NAKAJIMA)

		INCIDENCE OF CATARACT AMONG RELATIVES OF PROPOSITI				
		One or both parents affected	*Sibs only affected*	*Other relatives affected*	*Sporadic cases*	*Total*
Number of families		165	125	113	637	1040
Parents of propositi	First cousins, %	6.7	39.2	23.9	15.9	18.1
	Otherwise related, %	5.5	13.8	8.8	5.6	7.0
	Total consang., %	12.2	53.0	32.7	21.5	25.1

the rate of first-cousin marriages is the highest (39.2 percent), strongly suggesting an autosomal recessive inheritance. Nakajima suspects that one or several recessive genes are responsible for nearly 36 percent of congenital cataract in Japan.

Similar intensive studies on other common abnormalities, including congenital malformations (see p. 148), will eventually furnish the key to the complexity of the genetic causation of these afflictions.

BIBLIOGRAPHY

Morton, N. E., Non-randomness in consanguineous marriage, *Ann. Human Gen., 20,* 1955, 116-134.

Shields, J., and Slater, E., An investigation into the children of cousins, *Acta Genet. Stat. Med., 6,* 1956, 60-79.

Tanaka, K., Estimation of the frequency of partially sex-linked genes in man, *Am. J. Human Gen., 7,* 1955, 163-169.

Nakajima, A., Congenital and hereditary blindness in Japan, Transactions, First Congress Asia Pacific Academy of Ophthalmology, Manila, 1960, pp. 109-137.

Nakajima, A., and Takano, E., Survey of congenital cataract among inmates of blinds' schools, *Rinsho Ganka (Clinical Ophth.)4, 1,* 1960, 1769-1772.

NEEL: Thank you, Dr. Tanaka, for your most interesting contribution. Dr. Sutter will now take the chair.

SUTTER: The next paper, also dealing with Japanese populations, will be a discussion of the various pitfalls that the population geneticist may encounter when attempting to calculate the frequency of an unevenly distributed recessive gene.

J. V. NEEL, H. B. HAMILTON,
T. Y. KOBARA, K. OZAKI*

The Uneven Distribution in Japan of Carriers of the Rare Recessive Gene Causing Acatalasemia and the Implications for Studies on Inbreeding Effects

Although it is increasingly recognized that many rare recessive genes have effects in the heterozygous state which can be detected by suitable laboratory tests, there is a real paucity of information concerning the actual distribution in populations of the heterozygotes for rare recessives. Until quite recently, quick and accurate survey methods have not been available for studying actual heterozygote distributions in the case of rare recessive genes. This paper will describe what the

* The authors of this paper are members of the Atomic Bomb Casualty Commission, a field research agency of the National Academy of Sciences—National Research Council. The Commission is supported by the U.S. Atomic Energy Commission and is administered in cooperation with the National Institute of Health of the Japanese Ministry of Health and Welfare.

development of a method for detecting the carriers of a particular rare recessive revealed in Japan. The implications of these findings for certain basic genetic problems will be briefly explored. It is felt that some of these implications are relevant to the interpretation of types of studies it would be especially appropriate to pursue in Israel.

The trait in question is acatalasemia, a recessively inherited condition characterized by the absence of detectable tissue catalase activity.[1] Heterozygotes for this gene have been shown to exhibit approximately half-normal values of catalase activity. In a previous paper[2] it was noted that the application of a standard genetic

TABLE I

THE FREQUENCY OF HYPOCATALASEMIA IN FIVE DIFFERENT SURVEYS

Population	*Investigator*	*No. examined*	*No. hypo-catalasemic*	*Frequency of hypocatalasemia*
Hiroshima Japanese	Neel *et al.*, this paper	10,679	10*	0.000936
Nagasaki Japanese	Hamilton *et al.*, this paper	2,968	1	0.000337
Okayama Japanese	Takahara, 1961	1,500	0	0.000000
Nagano Japanese	Takahara, 1961	1,975	30	0.015190
Shimane Japanese	Takahara, 1961	618	6	0.009709

* Includes one mother-daughter pair.

formula due to Dahlberg[3] led to an estimate of the gene frequency, q, of 0.003, from which the frequency of homozygotes was calculated to be 0.00002, and of heterozygotes, 0.006—*i.e.*, 2 and 600 per 100,000 Japanese, respectively.

A rapid screening test has now been developed for the detection of the carrier state, termed hypocatalasemia. The results of 13,647 tests in Hiroshima and Nagasaki are shown in Table I. Also shown in this table are the findings of Takahara, using our technique, in three other regions—namely, Okayama, Nagano, and Shimane, the former being a large seacoast city located on the east coast of Honshu, and the latter two mountainous and somewhat isolated areas in central Honshu. Nagasaki, Hiroshima, and Okayama do not differ significantly from one another and combined yield a gene frequency of 0.0004. Nagano and Shimane differ in gene frequency from the other three areas and combined yield a gene frequency of 0.0069.

It is of interest to contrast these actual findings with the results of predicting

1 Takahara, S., Progressive oral gangrene probably due to lack of catalase in the blood (acatalasaemia), *Lancet, 2,* 1952, 1101-1104.

2 Takahara, S., Hamilton, H. B., Neel, J. V., Kobara, T. Y., Ohgura, Y., and Nishimura, E. T., Hypocatalasemia: a new genetic carrier state, *J. Clin. Invest., 39,* 1960, 610-619.

3 Dahlberg, G., On rare defects in human populations with particular regard to inbreeding and isolate effects, *Proc. Roy. Soc. Edinburgh, 58,* 1938, 213-232.

gene frequency using the well-known Dahlberg formula,[4] or the more recent and lesser known but superior formula of Kimura.[5] If I may refresh your memories, Dahlberg's formula is as follows:

$$q = \frac{c(1-k)}{16k - 15c - ck}, \tag{1}$$

with the frequency of heterozygotes then calculated from the relationship

$$\text{frequency of heterozygotes} = 2q(1-q)(1-a) \tag{2}$$

where

q = the frequency of the recessive gene responsible for acatalasemia,
c = the proportion of first-cousin marriages among the population as a whole, assumed from previous studies in Japan[6] to be 0.06,
k = the proportion of first-cousin marriages among the parents of homozygous individuals, assumed from the data on 17 sibships[7] to be 0.59, and
a = the coefficient of inbreeding for the population, assumed from previous studies[8] to be 0.004.

Kimura has now derived a more generalized formula and also a formula for the variance of the estimate, which has the advantage of utilizing all the available data, as follows:

$$v_o \sum_{i=o} \frac{u_i}{x + (1-x)f_i} = \frac{u_o}{x}, \quad \text{and} \tag{3}$$

$$V_{\bar{x}} = \frac{\frac{1}{M}\left\{\left(\frac{v_o - 1}{x}\right)^2 u_o + v_o^2\left[\left(\frac{16}{1+15x}\right)^2 u_1 + \left(\frac{32}{1+31x}\right)^2 u_2 + \cdots\right]\right\} + \frac{u_o^2(1-v_o)}{v_o x^2 N}}{\left\{v_o\left(\frac{u_o}{x^2} + \frac{15\cdot 16 u_1}{(1+15x)^2} + \frac{31\cdot 32 u_2}{(1+31x)^2} + \cdots\right) - \frac{u_o}{x^2}\right\}^2} \tag{4}$$

where

x = the frequency of the recessive gene in question,
f_i = the coefficient of inbreeding for the children of the sibships in which the recessive defect occurs ($f_0 = 0$ for unrelated parents, $f_1 = 1/16$ for first cousins, etc.)
m_i = number of sibships yielding recessive individuals in which a particular f_i obtains,
M = total number of sibships in which the recessive trait has been reported ($= m_0 + m_1 + m_2 + \cdots$),
$u_1 = m_1/M$, and

4 *Ibid.*
5 Kimura, M., Theoretical basis for the study of inbreeding in man, *Jap. J. Human Gen., 3,* 1958, 51-70.
6 Neel, J. V., Kodani, M., Brewer, R., and Anderson, R. C., The incidence of consanguineous matings in Japan, *Am. J. Human Gen., 1,* 1949, 156-178.
7 Takahara, S., Hamilton, H. B., Neel, J. V., Kobara, T. Y., Ohgura, Y., and Nishimura, E. T., *loc. cit.*
8 Neel, J. V., Kodani, M., Brewer, R., and Anderson, R. C., *loc. cit.*

v_0 = the proportion of sibships resulting from nonconsanguineous marriage in the population at large, assumed for these data to be 0.90.

The application of Dahlberg's formula to the 17 sibships in which acatalasemia has been observed to be segregating yields a gene-frequency estimate of 0.003. With Kimura's formula, the frequency is calculated to be 0.00082, with a standard error of 0.0053. The standard error of the estimate is relatively very large, and because of its size the values for q yielded by these two formulas do not differ significantly from one another or from the actual survey results, even though the results for Hiroshima-Nagasaki-Okayama combined differ significantly from those for Nagano-Shimane combined. We estimate that it would require at least 100 additional segregating sibships to narrow the variance term down to where comparisons between observation and prediction begin to become meaningful.

Now, as is well known, there are many assumptions underlying the use of these formulas. One of the chief of these is of a uniform gene frequency throughout the area being studied. In our opinion, our demonstration of a nonuniform frequency raises some very serious questions for the use of such formulas. Let us consider how local variations in gene frequency can lead us astray.

Out of a multitude of possible illustrative models, two simple alternatives may be considered. These alternatives are certainly abstractions in that, although they represent a step toward biological realities, they are still gross oversimplifications. Without these oversimplifications, however, the principal point could be buried in a mass of mathematical details.

Let us assume that in a group of 10,000 individuals there occurs a completely neutral and completely recessive gene. This gene is limited to three extended kindreds, in each of which 10 (heterozygous) members possess it. This group moves into a new and favorable geographic area. Circumstances are such that this group immediately becomes subdivided into three subgroups ("neighborhoods") comprising, respectively, 10, 20, and 70 percent of the population, with differing rates of inbreeding and with no exchange of members. It may be assumed that at the time such a group first moves into an area and distributes itself to occupy the desirable portions of the new territory, biologically related individuals (kindreds) will tend to remain together. We will postulate that in the smallest group, 10 percent of all marriages involve first cousins ($c = 0.10$), whereas in the intermediate group the frequency of first-cousin marriages is 5 percent and, in the largest group, 1 percent. In time all subgroups undergo a 100-fold increase in numbers, so that the total population becomes 1,000,000, with gene carriers increasing proportionately. No further mutations resulting in this particular gene occur, and there is assumed to be no genetic drift.

Let us now explore the consequences for estimates of q from c and k (formula 1) of the location of the three kindreds carrying the hypothetical gene. In model 1 it is assumed that one of these kindreds finds a place in each of the three "neigh-

borhoods." In model 2, it is assumed that all three kindreds come to reside in the largest "neighborhood." The differences which these accidents of distribution can introduce into estimates of q *as calculated from the over-all average of* c *and* k are shown in Table II. For each of the subpopulations, k has been derived by substitution of the given values of q and c in formula 1. Then, as would be the case in most attempts to calculate gene frequencies, an average value of c ($c_{av.}$) and k ($k_{av.}$) for the entire population has been obtained. It is apparent that the esti-

TABLE II

COMPARISON OF CALCULATIONS FOR THE FREQUENCY, q, OF A RARE RECESSIVE GENE IN TWO CONTRASTING POPULATION MODELS

Percentage of population	q	c	k
MODEL 1			
10	0.0050	0.10	0.60
20	0.0025	0.05	0.58
70	0.000714	0.01	0.48
	$q_{av.} = 0.0015$	$c_{av.} = 0.027$	$k_{av.} = 0.59$
	$q_{calc.} = 0.0012$		
MODEL 2			
10	0.0	0.10	—
20	0.0	0.05	—
70	0.00214	0.01	0.24
	$q_{av.} = 0.0015$	$c_{av.} = 0.027$	$k_{av.} = 0.24$
	$q_{calc.} = 0.0060$		

mates of q ($q_{calc.}$) resulting from substitution of the *average* value of c and k in formula 1 differ for the two models by a factor of 5.

Although this particular example is undoubtedly somewhat extreme in the disparity in the degree of inbreeding in the subpopulations, as well as the rarity of the gene concerned and the simplifying assumptions which are made regarding the characteristics of the population, it is clear that lesser disparities, such as can even exist within a single Japanese city,[9] can easily result in calculations differing by a factor of 2 or 3. It should be re-emphasized that these are vastly oversimplified models, chosen from a multitude of possibilities, but a variety of other models would serve to make the same point of the influence of population structure on gene-frequency estimates. Furthermore, only one of several ways in which populations may depart from the model have been considered here. Other possible disturbing influences include such factors as fertility differentials, recent relaxation of inbreeding, and assortative mating.

9 Schull, W. J., A note on consanguineous marriages in the cities of Hiroshima and Nagasaki, *Jap. J. Human Gen.*, *3*, 1958, 33-37.

These simple models have some interesting implications for attempts to utilize inbreeding effects for a variety of computations.[10] Returning to the situation described above, assume that the trait associated with this hypothetical recessive gene is readily identifiable, so that it would be scored in studies on inbreeding effects. Further, assume only two types of marriage in the two populations—namely, between first cousins or between unrelated individuals and, for this generation, stability in population numbers. The frequency of appearance of affected individuals from the two types of marriage in consequence of the two different models of population structure has been computed in Table III. In the first case, the ratio of proportion of affected from first-cousin marriages to proportion affected from nonconsanguineous marriages is approximately 49, whereas in the second case it is approximately 10. Stated in terms of the ratio of the "inbred load" to the "randomly mating load" of Morton *et al.*,[11] these correspond to ratios of 763 and 151, respectively.

The significance of a knowledge of population structure for attempts to calculate "mutational" vs. "segregation" loads is thus obvious, but will not be discussed in detail at this time. However, it may be noted that this factor has been inadequately dealt with in some current treatments of the subject.[12] It should also be apparent from the model that conclusions regarding the number of loci at which there may occur recessive genes with a given phenotypic effect (*e.g.*, deaf mutism) which are based upon an apparent discrepancy between the observed frequency of the phenotype and the frequency of consanguinity among the parents of affected individuals may also be biased by this "neighborhood effect." The bias can be of such a degree that, for the present, attempts on the basis of consanguinity data to estimate the number of recessive genes capable of producing a given phenotype, and the deductions drawn therefrom,[13] cannot be taken very seriously, a fact which if not already apparent on theoretical grounds would be suggested by the wide discrepancy between calculations based on the data of Lindenov (1945) from Denmark[14] and Stevenson and Cheeseman (1956) from North Ireland.[15] In this connection, it should be noted that the method Dr. Steinberg has presented (p. 140) may avoid some of these problems.

I fear that some in this audience will feel I have delved too deeply into the minutiae of population genetics. The fact is, however, that the estimation of

10 Morton, N. E., Crow, J. F., and Muller, H. J., An estimate of the mutational damage in man from data on consanguineous marriages, *Proc. Nat. Acad. Sci., 42,* 1956, 855-863.
11 *Ibid.*
12 Morton, N. E., The mutational load due to detrimental genes in man, *Am. J. Human Gen., 12,* 1960, 348-364.
13 Chung, C. S., Robison, O. W., and Morton, N. E., A note on deaf mutism, *Ann. Human Gen., 23,* 1959, 357-366.
14 Lindenov, H., *The Etiology of Deaf-mutism with Special Reference to Heredity,* Opera ex Domo Biol. Hered. Humanae Univ. Hafniensis, Vol. 8, E. Munksgaard, Copenhagen, 1945, p. 268.
15 Stevenson, A. C., and Cheeseman, E. A., Hereditary deaf mutism, with particular reference to Northern Ireland, *Ann. Human Gen., 20,* 1956, 177-231.

TABLE III

A COMPARISON OF THE CONSEQUENCES OF FIRST-COUSIN MARRIAGE IN TWO POPULATION MODELS

q = gene frequency, F = coefficient of inbreeding for first-cousin marriages—namely, 0.06—and n and n' refer to size of subpopulations. The frequency of homozygotes resulting from the marriage of first cousins is $qF + q^2(1 - F)$ (*i.e.*, cols. 3 + 5), whereas the frequency from the marriage of unrelated persons is simply q^2 (col. 9).

MODEL 1

	FIRST-COUSIN MARRIAGES						MARRIAGES OF UNRELATED PERSONS			
Percent	*Total no. (n)*	*qF*	*qFn*	$q^2(1 - F)$	$q^2(1 - F)n$	*Total aff.*	*Total no. (n′)*	q^2	q^2n'	*Total*
10	100,000 × 0.1 = 10,000	(.005)(.06) = .00030	3	$(.005)^2(.94)$ = .000024	.24	3.24	90,000	.000025	2.25	5.49
20	200,000 × 0.05 = 10,000	(.0025)(.06) = .00015	1.5	$(.0025)^2(.94)$ = .00000588	.06	1.56	190,000	.00000625	1.18	2.74
70	700,000 × .01 = 7,000	(.000714)(.06) = .0000428	.300	(.000714)(.94) = .000000479	.00335	.303	693,000	.000000510	.353	.656
Total	27,000					5.10	973,000		3.78	

Incidence, 1st cousins $= \frac{5.10}{27,000} = .00018889$

Incidence, unrelated $= \frac{3.78}{973,000} = .00000388$

Ratio $= \frac{.00018889}{.00000388} = 48.68$

MODEL 2

	FIRST-COUSIN MARRIAGES						MARRIAGES OF UNRELATED PERSONS			
Percent	*Total no. (n)*	*qF*	*qFn*	$q^2(1 - F)$	$q^2(1 - F)n$	*Total aff.*	*Total no. (n′)*	q^2	q^2n'	*Total*
10	10,000	0	0	0	0	90,000	90,000	0	0	0
20	10,000	0	0	0	0	0	190,000	0	0	0
70	7,000	(.00215)(.06) = .000129	.9	$(.00215)^2(.94)$ = .00000434	.03	.93	693,000	.0000046225	3.2	4.13
Total	27,000					.93	973,000		3.2	

Incidence, 1st cousins $= \frac{.93}{27,000} = .00003444$

Incidence, unrelated $= \frac{3.2}{973,000} = 0.00000329$

Ratio $= \frac{.00003444}{.00000329} = 10.47$

gene frequencies and the interpretation of inbreeding results are central problems in this field. Here in Israel you are in a position to collect most unusual data in this respect. Accordingly, it has seemed worth while to draw your attention to some of the very real problems that may arise in utilization of these data.

NEEL: The last of the scheduled papers of this morning will be delivered by Dr. Goldschmidt.

E. GOLDSCHMIDT, T. COHEN,
N. BLOCH, L. KELETI, S. WARTSKI

Viability Studies in Jews from Kurdistan*

The Kurdish Jews are one of several Oriental communities among whom consanguineous unions are still commonly practiced although an increasing proportion of their members elect their marriage partners from other ethnic groups.[1]

Our choice of the Kurdish Jews for viability studies in offspring of different mating systems was directed by several considerations. The community is well defined by its origin from the mountainous area of Kurdistan which is today politically divided among Iraq, Persia, and Turkey (see map, p. 343). It is distinguished by an old tradition. Until quite recently the majority of Kurdish Jews spoke "Targum," a variety of the Aramaic of Ancient Babylon and Palestine, as their main language in addition to Kurdish or Arabic, required for communication with their non-Jewish neighbors. A considerable number of Kurdish Jews entered Palestine during the 'twenties and 'thirties of the present century. These old-timers, who have now been settled in Israel for more than a generation, were joined in 1951 by a much larger wave of immigrants comprising nearly all of those who had stayed behind in Kurdistan.

In Jerusalem the new immigrants and the old-timers live today in the same quarters, all under very similar socioeconomic conditions but differing in one respect—the length of the family's experience with modern medical care. Most couples feel bound to this day by a strict tradition barring any attempt at limiting family size. In addition to all these factors which facilitate viability studies, we were encouraged by the cooperative and communicative attitude of the Kurdish families during home interviews and medical examinations of the children.

* This research was supported in part by a grant from the Ford Foundation.

1 Goldschmidt, E., Ronen, A., and Ronen, I., Changing marriage systems in the Jewish communities of Israel, *Ann. Human Gen. London, 24,* 1960, 191-204.

The families are identified by reference to the files of the Mother-Child Welfare Centers, which are under the direction of the Hadassah Organization in the areas surveyed by us. These files list all the children of each family and also contain comprehensive medical data on children born in Israel. Miscarriages, stillbirths, and deaths are likewise recorded. Prior to the home interview an abstract of the file is prepared. The interview begins with questions relating to the recorded data. It is thus easy to verify the accuracy and comprehensiveness of the parents' responses to the interview. Reliability is essential because of the unrecorded information they have to supply regarding their bihrtplaces in Kurdistan and any consanguinity between them or their parents. These data can, however, usually be cross-checked by independent interviewing of their sibs and parents.

The average interview lasts from one to two hours. Most families are visited at least twice in order to collect information from other family members or to examine children who were absent during the first visit.

In accordance with their genetic affinity, the couples are grouped into five classes. The centers of Jewish settlement in Kurdistan are distributed over three countries (see map, p. 343). Marriages between partners born in the same country are considered *endogamous*. The endogamous couples include first cousins, more distant relatives and unrelated partners. Marriages between partners born in different centers of Kurdistan are classed as *exogamous,* whereas the *interethnic* union between a Kurdish Jew and a member of a different community constitutes a more extreme degree of outbreeding.

We have thus far studied two samples of Kurdish Jews, one in an immigrant village in the Jerusalem corridor, the other in one of the older quarters of the City of Jerusalem. Except for the group "endogamous unrelated," all classes are still fairly small and will have to be increased before justifying definitive conclusions on viability effects of the different mating types. The main interest of the present material may derive from the fact that it contains a rather detailed record of the family of endogamous unrelated Kurdish Jews.

Nevertheless, we should like to invite discussion on a trend which is observed on comparing the different classes of marriages in this material. This trend concerns the miscarriage rate, which appears negatively correlated with the degree of consanguinity in both samples investigated by us (see Fig. 33). It should be stressed that in the immigrant village there was no evidence of voluntary abortions. In the Jerusalem district a small proportion of such interventions was reported by the mothers, and these cases have been excluded from our calculations. If many voluntary abortions had been falsely reported as spontaneous, the trend observed by us might merely reflect a high correlation between the tendency to consanguineous and other endogamous marriages and the tradition-bound avoidance of any form of "family-planning." This assumption appeared most unlikely in view of the frankness with which both voluntary abortions and spontaneous miscarriages were admitted and also because of the records on hospitalization following most miscarriages.

We therefore incline to the view that the effect observed by us may have a biological rather than a sociological basis. It was pointed out long ago by Dr. Stern[2] that cousin families run a smaller risk of Rhesus incompatibility than unrelated couples. His considerations apply equally to other types of incompatibility. The role of many immunological systems, including even the familiar ABO groups in pregnancy wastage, is only just beginning to be understood (see p. 45). The importance of many other antigenic systems will probably be demonstrated in the future (see p. 264).

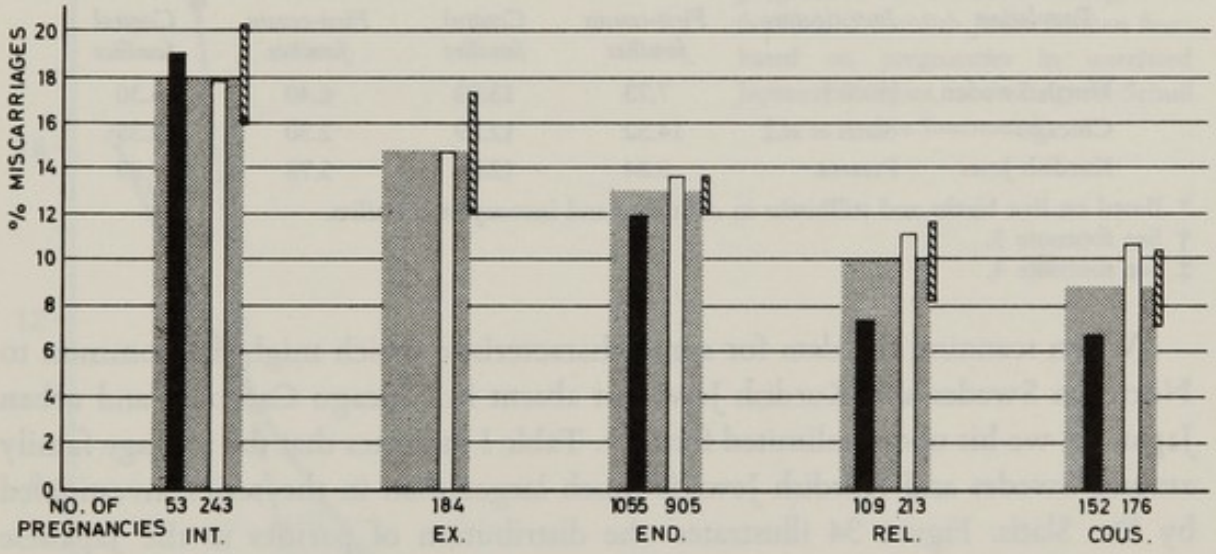


FIG. 33. The rates of miscarriages in various types of families among Kurdish Jews. Miscarriage rates are indicated by heights of bars. Black bars: immigrant village; white bars: City of Jerusalem; shaded bars: both samples combined; hatched vertical lines: extent of $\pm$ 1 Standard Error for combined samples.
Int: interethnic; Ex: exogamous; End: endogamous, unrelated; Rel: relatives remoter than first cousins; Cous: first cousins and closer relationships.

When examining the miscarriage rates observed by other workers in similarly intensive studies of consanguineous families (Table I), we noted that Dr. Böök's[3] results from Sweden showed the best agreement with our own and that the cousin families of his sample appeared, indeed, to enjoy an advantage in this respect. In the consanguineous Chicago families investigated by Dr. Slatis,[4] no such advantage was apparent, but their miscarriage rate was virtually identical with that of unrelated couples. The small excess of miscarriages and stillbirths in the cousin families of Chicago was nonsignificant.

Slatis, like Schull,[5] inclines to the view that the increased risk of cousin children

2 Stern, C., and Charles, D. R., The rhesus gene and the effect of consanguinity, *Science, 101,* 1945, 305-307.
3 Böök, J. A., Genetical investigation in a North Swedish population: The offspring of first-cousin marriages, *Ann. Human Gen. London, 21 (3),* 1957, 191-221.
4 Slatis, H. M., Reis, R. H., and Hoene, R. E., Consanguineous marriages in the Chicago region, *Am. J. Human Gen., 10,* 1958, 446-464.
5 Schull, W. J., Empirical risks in consanguineous marriages: sex ratio, malformation, and viability, *Am. J. Human Gen., 10,* 1958, 294-343.

becomes hardly manifest during intrauterine life. These authors offer no explanation for the apparent absence of recessive lethals acting during the embryonic and fetal periods, nor do they resort to Stern's theory dealing with the "incompatibility load" (see p. 235) of outbred families which might obscure a lethal load of similar extent acting during prenatal life in the offspring of first cousins.

TABLE I

FERTILITY AND MISCARRIAGE RATES IN VARIOUS POPULATIONS STUDIED FOR CONSANGUINITY EFFECTS

		MISCARRIAGE RATE PERCENT		AVERAGE NUMBER OF BIRTHS* PER FAMILY	
Population	*Investigators*	*First-cousin families*	*Control families*	*First-cousin families*	*Control families*
North Sweden	Böök†	7.73	13.92	6.40	5.30
Chicago	Slatis *et al.*‡	14.52	12.89	2.30	2.35
Kurdish Jews	Present	8.84	12.86	5.75	5.89

* Based on live births and stillbirths in complete and incomplete families.
† See footnote 3.
‡ See footnote 4.

When scanning the data for some characteristic which might be common to Northern Swedes and Kurdish Jews but absent in Chicago Catholics and urban Japanese, we hit upon unlimited fertility. Table I indicates that the average family among Swedes and Kurdish Jews is much larger than in the series investigated by Dr. Slatis. Figure 34 illustrates the distribution of parities in the Japanese sample as compared with our own. Among Kurdish Jews the fifth and later parities constitute more than 50 percent of all pregnancies, whereas in the Japanese cities sampled these higher parities amounted to only 15 percent. Such fertility differentials should certainly influence the extent of pregnancy wastage due to incompatibility effects in the majority of antigenic systems. In general the risk of the wife's building up immunity against some antigen of her husband increases with each pregnancy, although this may not apply to the AB systems. Figure 35 shows the well-known rise in abortion risk with advancing birth rank; Figures 36 and 37 indicate that the increased miscarriage rate in the outbred marriages of the Jerusalem sample was due mainly to the higher birth orders.

Brief mention should be made of another trend which was apparent in the five classes of families studied. This trend concerns the sex ratio (see Fig. 37), which varied, much to our surprise, in accordance with the prediction made long ago by Prof. Haldane[6] and discussed at length by Macklin.[7] It is well known that Haldane's theory regarding the increased sex ratio in cousin children hinges upon the assumption that partial sex linkage exists in humans. More recently cytolo-

6 Haldane, J. B. S., and Moshinsky, P., Inbreeding in Mendelian populations with special reference to human cousin marriage, *Ann. Eug. London, 9,* 1939, 321-340.
7 Macklin, M. T., Sex ratios in partial sex linkage. I. Excess of affected females from consanguineous matings, *Am. J. Human Gen., 4,* 1952, 14-30.

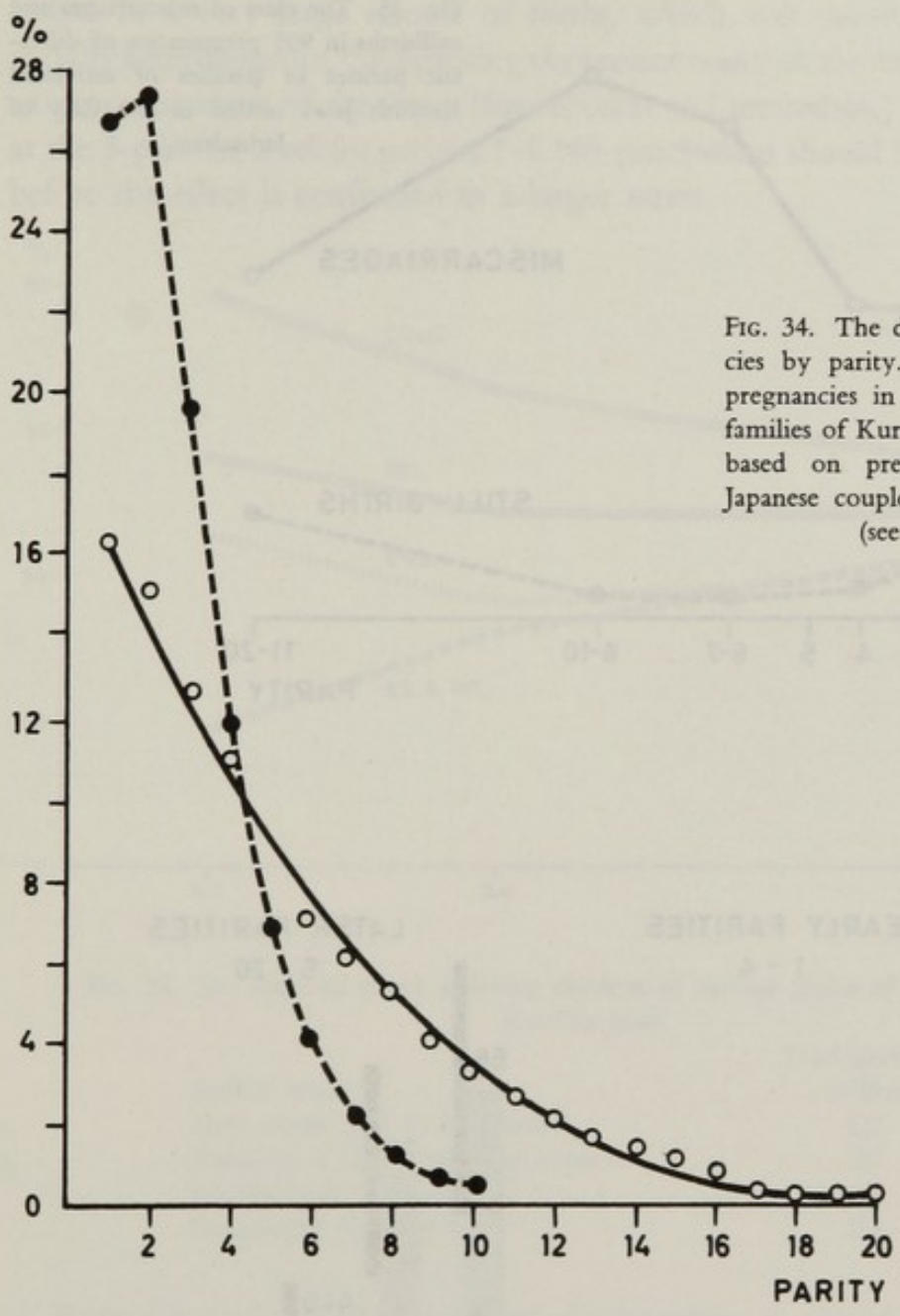


FIG. 34. The distribution of pregnancies by parity. Solid line: based on pregnancies in unrelated endogamous families of Kurdish Jews: broken line: based on pregnancies in unrelated Japanese couples, according to Schull (see footnote 5).

gists have tended to assume that the X and Y chromosomes of man do not form chiasmata and that their pairing in meiosis is of a nonspecific character. The existence of true chiasmata between the X and Y has, however, been confirmed in certain mammals.[8,9] Failing partial sex linkage, an inbreeding effect on the sex ratio might be due to the suppression by the Y chromosome of X-linked recessive lethals. Such a phenomenon has recently been described in Drosophila.[10]

Complex effects of parity and parental ages on the sex ratio have been des-

8 Matthey, R., La formule chromosomique de *Macrotarsomys bastardi* et le problème des Nesomyinae, *Bull. Res. Council Israel, 10 B,* 1961, 1-6.

9 Wahrman, J., and Ritte, U., Pre- and post-reduction in Apodemus, personal communication, 1962.

10 Lindsley, D. L., Edington, C. W., and Von Halle, E. S., Sex-linked recessive lethals in Drosophila whose expression is suppressed by the Y chromosome, *Genetics, 45,* 1960, 1649-1670.

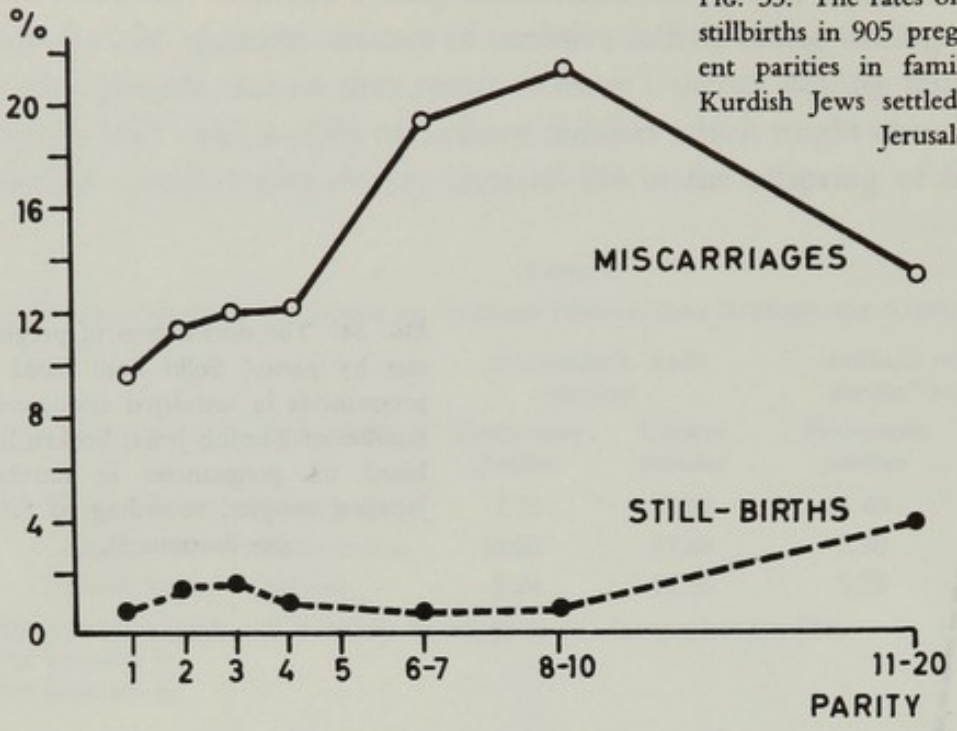


FIG. 35. The rates of miscarriages and stillbirths in 905 pregnancies of different parities in families of unrelated Kurdish Jews settled in the City of Jerusalem.

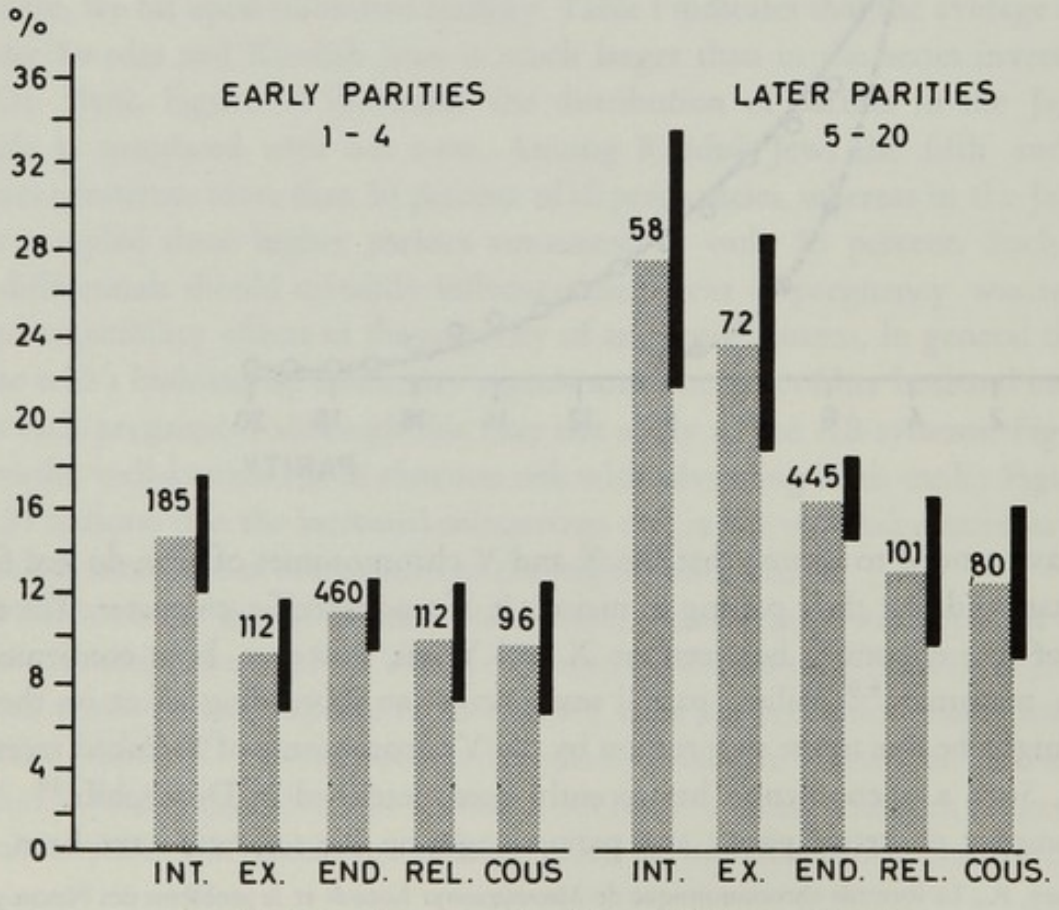


FIG. 36. Miscarriage rates in earlier and in later parities in families of Kurdish Jews settled in the City of Jerusalem. Types of marriages indicated by Int.-Cous. as in Figure 33.

cribed in a very large sample of births, which was, however, ethnically and socially heterogeneous.[11] Regarding the present material, the difference between the extreme members of the series (first cousins and interethnic) is barely significant at the 5-percent level for parities 1-4. No conclusions should be drawn, therefore, before the effect is confirmed in a larger series.

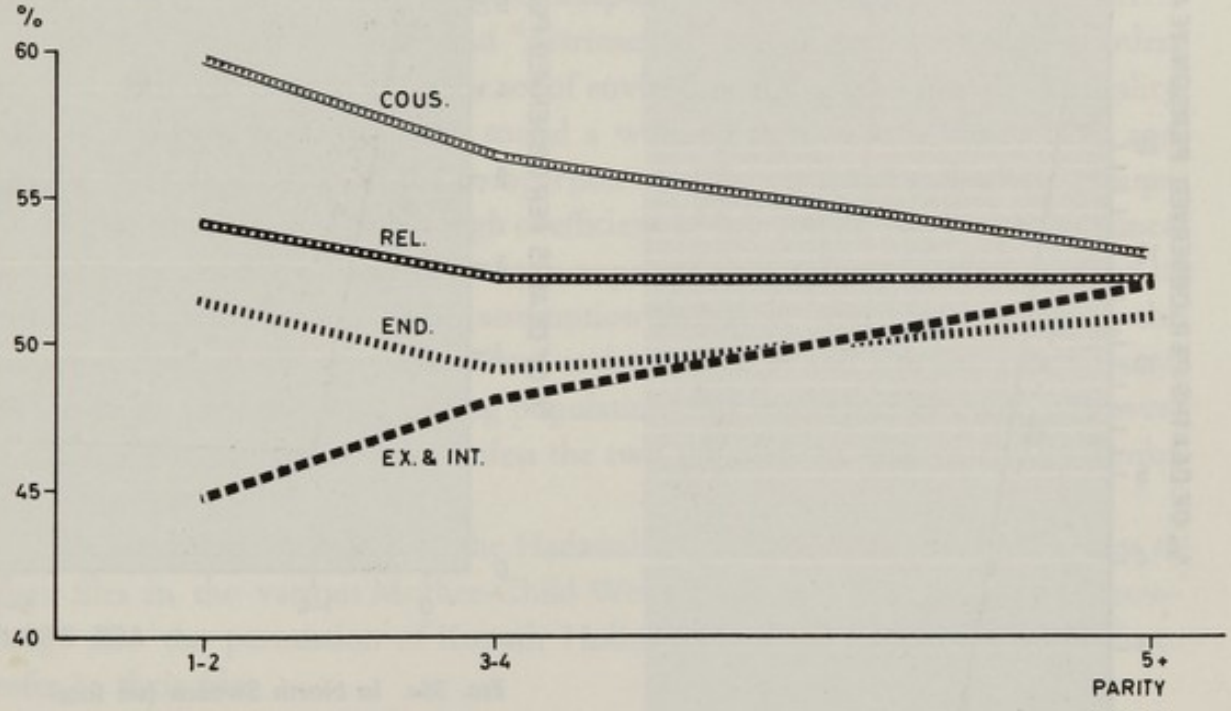


FIG. 37. Sex ratio by parity in living children of various classes of couples among Kurdish Jews.

Parents' union	*Total number of children*
First cousins and closer relatives	227
Relatives remoter than first cousins	237
Endogamous unrelated	1268
Exogamous + interethnic	363

Regarding other viability effects of inbreeding, it should be stressed that the present series has not thus far shown any significant excess of abnormality (malformations or chronic disease) in the cousin children (see p. 349), although in other intensive family studies[12, 13] such conditions could be shown to be significantly more common in the offspring of consanguineous unions.

The only significant difference between the cousin children and the controls of our sample concerns infant mortality. There were more deaths in consanguineous families in Kurdistan and in Israel during the "pre-antibiotic period," which terminated around 1944. Under conditions of modern medical care this disad-

11 Novitski, E., and Kimball, A. W., Birth order, parental ages, and sex of offspring, *Am. J. Human Gen.*, *10*, 1958, 268-275.

12 Böök, J. A., *loc. cit.*

13 Slatis, H. M., Reis, R. H., and Hoene, R. E., *loc. cit.*

FIG. 38*a-c*. Mortality per observed person-year in offspring of different types of unions. Solid lines: first cousins; broken lines: unrelated.

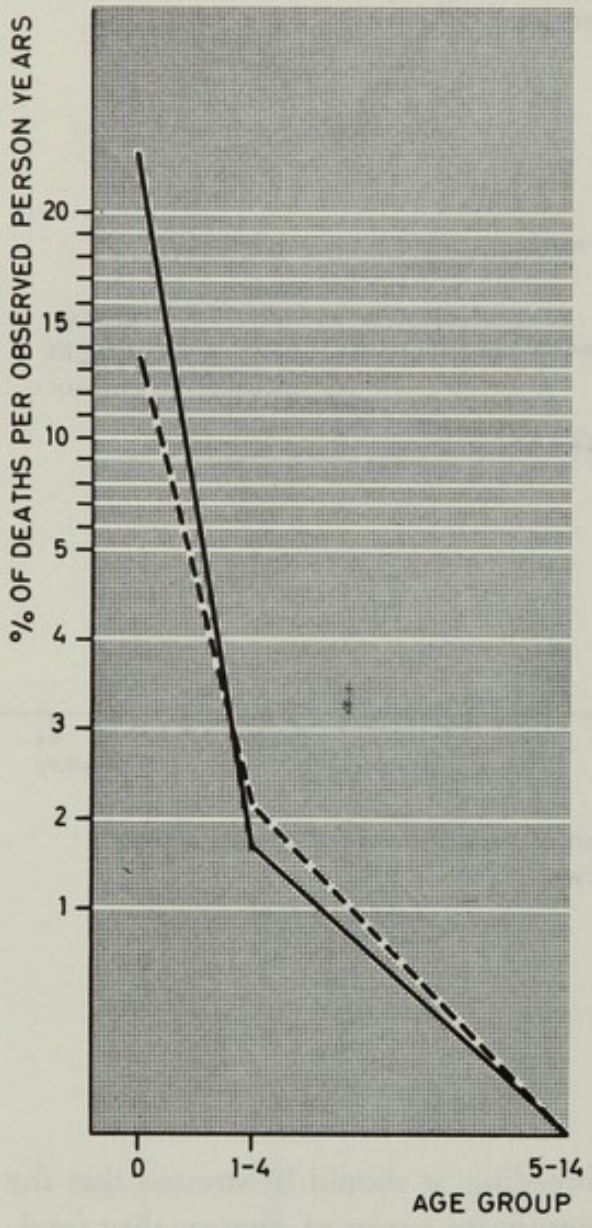


FIG. 38*b*. In children of Kurdish Jews born abroad or in Israel, observed during the period 1930-1944. Number of observed person-years: not related—3718; first cousins—660.

FIG. 38*c* (*at right*). In children of Kurdish Jews born in Israel, observed during the period 1945-1960. Number of observed person-years: not related—6974; first cousins—1074.

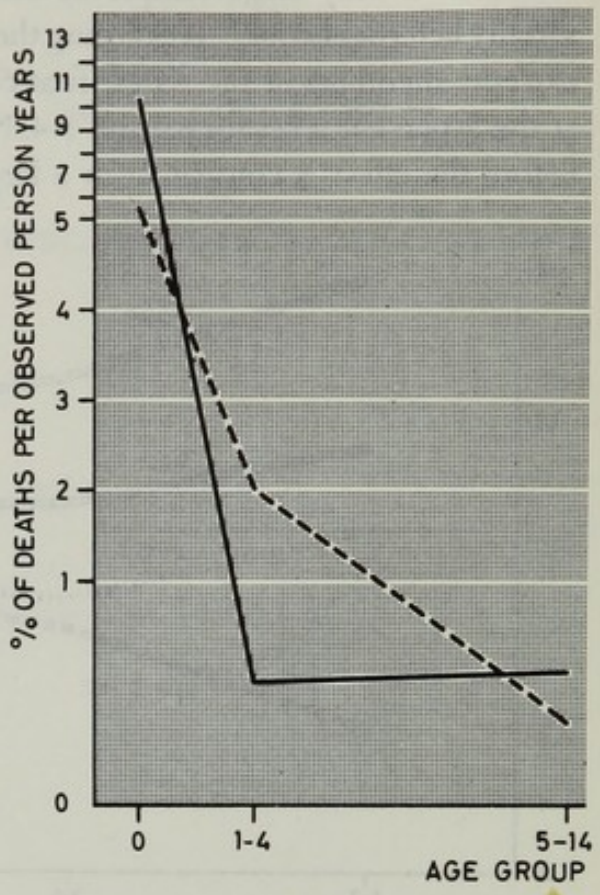
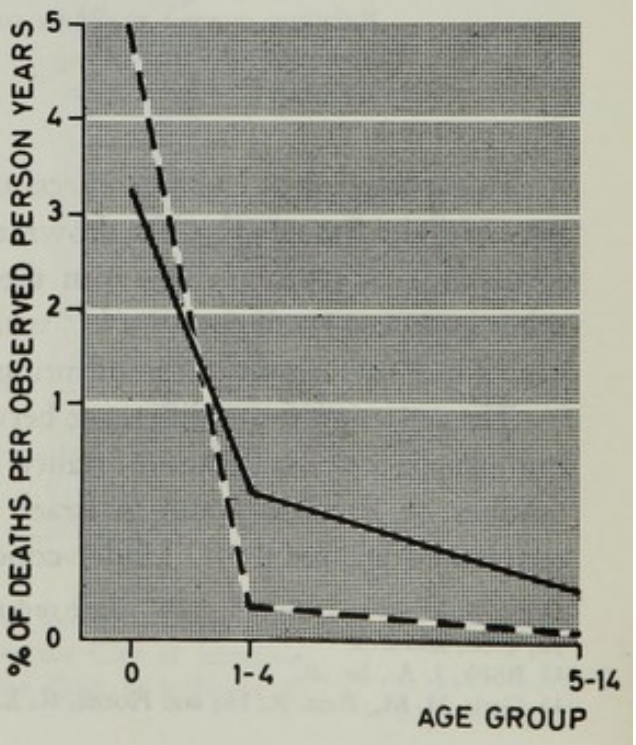


FIG. 38*a*. In North Sweden (see footnote 3). Number of observed person-years: not related—1539; first cousins—2482.



vantage of the cousin families could no longer be observed. Figure 38 illustrates the absolute and relative differences in infant mortality for these two periods among children of Kurdish Jews and in Dr. Böök's[14] sample, in which mortality ranged about midway between our two samples.

Two earlier sessions of this conference have amply demonstrated that a given genotype may exhibit a wide range of adaptive values in a series of different environments. The terms "lethal" and "detrimental" are, in fact, meaningless unless applied with reference to a specific set of environmental conditions. The mortality data of the present sample may sound a warning against such abstractions and against their application to the comparison of different social and ethnic groups.

In communities in which a high coefficient of inbreeding has been maintained for many generations, homozygosity is expected to involve a smaller risk than in large outbreeding groups. This assumption should be tested by comparing the consanguinity effects in small, inbred isolates, such as the Kurdish community, and in large, generally outbreeding populations. Such comparisons will, however, remain of limited significance unless the two populations exist in closely similar environments.

We are greatly indebted to the Hadassah organization for giving us access to their files in the various Mother-Child Welfare Centers. We gratefully acknowledge also the permission of Kupath Holim and of all Jerusalem hospitals to refer to their files.

KRIEGER: I would like to ask Dr. Goldschmidt whether the mean number of pregnancies is the same in all her subsamples. If one group had a lower mean number of pregnancies than another, its miscarriage rate would also be expected to be lower.

GOLDSCHMIDT: This is a very pertinent question, but the data do not conform to your expectations.

The average period elapsed after marriage at the time of the investigation was very similar for cousin families, more distant relatives, and unrelated couples (see Table II). These three classes of endogamous families are also in good agreement with regard to the average numbers of children (see Table III). The same does not apply to the exogamous and interethnic unions. These two types of marriage have recently been much in vogue but were comparatively rare in former years.

Our outbred families are, therefore, relatively younger and have as yet fewer children on the average than the endogamous couples. Nevertheless, the average interval between births is closely similar in all five classes of mating.

NEEL: Thank you. The speakers of this morning have presented a great deal of new and very interesting data which are certain to elicit a very lively discussion.

14 Böök, J. A., *loc. cit.*

TABLE II

NUMBERS OF YEARS ELAPSED AFTER MARRIAGE IN DIFFERENT CLASSES OF UNIONS AMONG KURDISH JEWS

	IMMIGRANT VILLAGE			JERUSALEM CITY			TOTAL		
Type of union	*No. families*	*Mean no. years*	±St.E.	*No. families*	*Mean no. years*	±St.E.	*No. families*	*Mean no. years*	±St.E.
First cousins	18	13.28	±1.57	28	15.11	±2.04	46	14.39	±1.38
More distant relatives	15	10.40	±1.18	31	15.68	±1.85	46	13.96	±1.35
Unrelated endogamous	121	13.07	±0.74	140	13.96	±0.81	261	13.55	±0.55
Exogamous	—	—	—	37	11.24	±1.52	37	11.24	±1.52
Interethnic	6	10.83	±3.38	68	7.54	±0.68	74	7.81	±0.68

TABLE III

AVERAGE NUMBERS OF BIRTHS* IN DIFFERENT CLASSES OF FAMILIES AMONG KURDISH JEWS

	IMMIGRANT VILLAGE			JERUSALEM CITY			TOTAL		
Type of union	*No. families*	*Mean no. births*	±St.E.	*No. families*	*Mean no. births*	±St.E.	*No. families*	*Mean no. births*	±St.E.
First cousins	24	5.92	±0.54	28	5.61	±0.64	52	5.75	±0.42
More distant relatives	19	5.32	±0.52	31	6.10	±0.73	50	5.80	±0.49
Unrelated endogamous	153	6.07	±0.76	140	5.69	±0.33	293	5.89	±0.20
Exogamous	—	—	—	37	4.24	±0.49	37	4.24	±0.49
Interethnic	9	4.78	±0.85	68	2.94	±0.28	77	3.16	±0.27

* Includes live and still births in complete and incomplete families.

SUTTER: I should like to add one remark on the subject of mortality rates, a problem which came up in connection with the papers on the mortality in consanguineous families in Japan and Israel and which will be discussed by Dr. Freire-Maia with reference to Brazil. I suggest that the rate of infant mortality be recalculated on a more biometric basis, using the Bourgeois-Pichat[1] method. By this method the endogenic fraction of infant mortality may be separated from the exogenic environmental fraction. A very large number of measurements on the demographic scale have shown this method to be most effective in distinguishing between biological and environmental factors.

Endogenic mortality comprises lethality due to various causes such as malformations, congenital debility, and maternal biological factors. In order to separate the two fractions of infant mortality, the Bourgeois-Pichat method may be applied either by way of calculation or graphically.[2] For consanguinity studies the interest of this procedure lies in the fact that endogenic mortality reflects biological factors, including heredity, much better than the total infant mortal-

1 Bourgeois-Pichat, J., De la mesure de la mortalité infantile, *Population, 1,* 1946, 53-68, *6,* 1951, 233-248, 459-480.

2 *Ibid.*

ity. In 1958[3] I was able to show that endogenic mortality was significantly higher in children of consanguineous marriages than in children of a control group. The relative mortality rate of the two groups up to the age of 30 was fairly similar This, however, was not true with respect to endogenic mortality, which was higher among the consanguineous group. Hence it would be of interest to calculate these rates with respect to the data presented. Also, so far as they are based on mortality, the calculations of Morton and Slatis (cf. pp. 230 and 240) for the estimation of lethal equivalents may be corrected by the Bourgeois-Pichat method.

NEEL: The next discussant will be Dr. Steinberg, who will present some data on the population structure of a religious isolate in the U.S.

STEINBERG: The religious isolate in the U.S. and Canada which we have been studying has already been mentioned, and the cholesterol levels of their members have been discussed (p. 138). Complete records of live births, marriages, and deaths are kept in each colony, and all individuals have modern medical care available to them. I shall present a few results obtained in our study of this remarkable group.

As I stated earlier, this religious group is Anabaptist Protestant, originally stemming from Switzerland. They settled between 1874 and 1877 in three colonies in southeastern South Dakota. One of the colonies was headed by a blacksmith, and the descendants of these people are known as Schmiedenleut; another was headed by a teacher, and their descendants are now known as Lehrerleut; the third was headed by a man by the name of Darius and their descendants are now known as Dariusleut. The original settlers comprised between 40 and 50 families with 15 surnames among them. There are still only 15 surnames in the population. Since World War I, there has been no intermarriage between individuals of colonies descended from the Schmiedenleut and those in the other two colonies.

When the number of members in a colony approaches 200, new land is bought and a group of families moves to it while the others stay behind. In this fashion, new colonies bud regularly from older ones. At present there are about 55 Schmiedenleut colonies. The two other subsects together comprise approximately another 55 colonies. We have been studying the Schmiedenleut subsect but have not yet visited all their colonies.

At present they tend to avoid first-cousin marriages, not only because these marriages are prohibited by law in the regions in which they are settled but also because they are aware of the possible untoward effects occasioned by this type of union.

Each colony has a preacher elected for life who functions as its vital statistician, recording births, deaths, and marriages. Many families also record the same data in their family Bibles. These serve as a cross check of the data. Our

3 Sutter, J., Recherches sur les effets de la consanguinité chez l'homme, *Biol. méd.*, *47*, 1959, 563-660.

information, therefore, is all recorded and not hearsay or recalled, with the exception of the data concerning stillbirths and miscarriages which, unfortunately, are not recorded. I might mention that we have records on these people going back to the beginning of the eighteenth century.

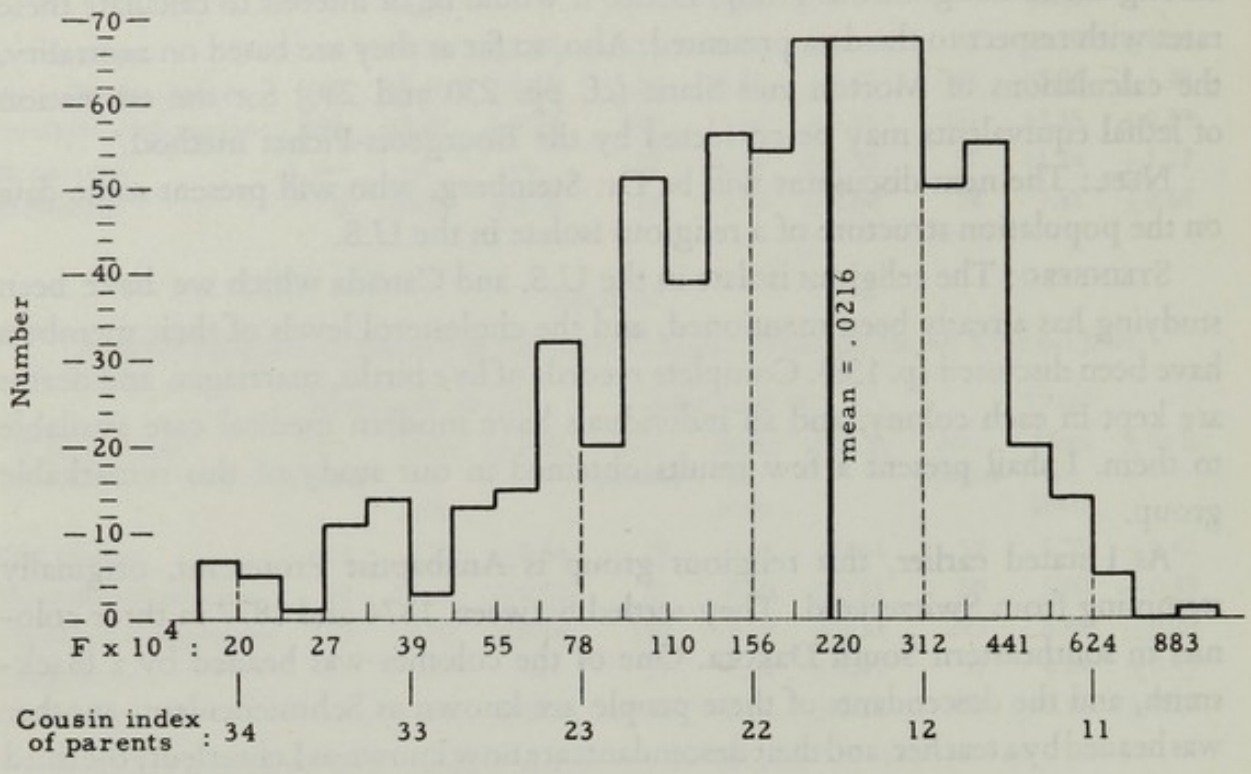


FIG. 39. Distribution of F (on a log scale) for the children of 667 families in a religious isolate. The distribution is based on one child per family (unpublished data of Mange and Steinberg).

The analyses I will present have been done by Mr. Arthur Mange. He calculated the inbreeding coefficients (F) (Fig. 39) for the children of 667 families. The unweighted mean of F equals 0.0216, lying between that of the offspring of first cousins once removed (0.0312) and that of second cousins (0.0156). Mange found a negative regression of height on F for males, significant at the 1-percent level; the regression coefficient for females is also negative but is not significant at this stage of the investigation (Table I). The ratio of male births was found to decrease fairly constantly with increasing birth order and this negative regression of sex ratio on birth order was significant (Table II). There is no regression of sex ratio on mother's age, or in contradistinction to Novitski and Kimball's data,[1] on father's age (Table III).

This at the moment is as far as the analysis has gone. I merely wanted to call the attention of the group to the fact that such a community does exist in the United States and that interesting data are being derived from it.

NEEL: The next contributor will be Dr. Leonard Kurland. He will discuss an isolate afflicted with a high incidence of severe neurological disorders.

1 Novitski, E., and Kimball, A. W., Birth order, parental ages, and sex of offspring, *Am. J. Human Gen.*, *10*, 1958, 268-275.

TABLE I

REGRESSION OF HEIGHT ON THE INBREEDING COEFFICIENT (F) OF INDIVIDUALS IN A RELIGIOUS ISOLATE*

		MEAN		
	No.	*Ht.*	*F*	*b*†
Males	212	67.7	.0255	—24.21‡
Females	209	62.8	.0261	—10.36

* Unpublished data of A. P. Mange and A. G. Steinberg.
† *b* in inches over entire range of F.
‡ $P < 0.01$.

TABLE II

REGRESSION OF SEX RATIO ON BIRTH ORDER*

	BIRTH ORDER								
	1-2	*3-4*	*5-6*	*7-8*	*9-10*	*11-12*	*13+*	*All*	*b*
Total	1131	1147	954	746	545	289	128	5120	
Sex ratio	.5202	.5118	.4874	.5040	.4734	.4429	.4453	.4986	—.0061†

* Unpublished data of A. P. Mange and A. G. Steinberg.
† $P < .01$.

TABLE III

REGRESSION OF SEX RATIO ON PARENT'S AGE*

	MOTHER'S AGE									
	<21	*21-24*	*25-28*	*29-32*	*33-36*	*37-40*	*41+*	*All*	*b*	*P*
Total	157	1064	1233	1022	772	552	320	5120		
Sex ratio	.5096	.5207	.5020	.5020	.5130	.4294	.4812	.4986	—.0110	~.1
	FATHER'S AGE									
	<25	*25-28*	*29-32*	*33-36*	*37-40*	*41-44*	*45+*			
Total	784	1192	1107	862	595	374	206	5120		
Sex ratio	.5230	.5134	.4950	.4919	.4403	.5027	.5291	.4986	—.0073	.3

* Unpublished data of A. P. Mange and A. G. Steinberg.

L. T. KURLAND

High Incidence of Neurological Disease in an Island Population

During the past few years the unusual incidence of neurological disorders among the indigenous Chamorro population of the Mariana Islands in the Western Pacific has been under study. Most of the investigations have centered on the island of Guam. I should like to review the earlier work, which suggested that amyo-

trophic lateral sclerosis is inherited, and call to your attention some of the more recent findings by a number of my colleagues which have cast some doubt on the earlier hypothesis. I will not have time to mention the names of the many people who have been concerned with this unusual geographic isolate, but several of our consultants are here today, among them our chairman.

Guam is a coral and volcanic island of about 225 square miles located 1500 miles east of the Philippines and about 1500 miles south of Japan. The Chamorros are a mixture of the original racial strain, presumably from southeast Asia, plus a heterogeneous addition of Spanish, Filipino, and others. A large number of U.S. military personnel and their dependents and a sizable group of construction workers from the Philippine Islands also inhabit Guam.

On Saipan, one of the smaller islands to the north, there are, in addition to the Chamorros, a small group of Carolinians who emigrated from the islands south of Guam at about the turn of the century and a few years later were resettled on Saipan.

Amyotrophic lateral sclerosis, which for the sake of convenience we refer to as ALS, is a progressive, fatal disorder of adults due to degeneration of the anterior horn cells in the spinal cord, the motor nuclei of the brain stem, and neurons in the motor cortex, with demyelination of the corticospinal and corticobulbar tracts.[1] Clinically, the disorder among the Chamorros, which is indistinguishable from that seen in other lands, is characterized by progressive muscle weakness and wasting and evidence of upper motor neuron disease. About 10 percent of the deaths in the adult Chamorro population are due to ALS.

The age and sex distribution of the affected on Guam is similar to that seen in other countries throughout the world. There is a preponderance of males, somewhat less than 2 to 1. Age distribution shows a range of 20 to 72 years, with a median age of about 45 years and about two-thirds occurring between 35 and 55 years. Most of the cases develop after the period of maximum reproduction. The average duration from recognized onset to death is about 3 to 4 years.[2-6]

Now for the picture of the frequency of the disease in other countries: In North America, the distribution of ALS mortality shows no variation by geographic region in the United States and Canada. The age-adjusted rates of several

1 Malamud, N., Hirano, A., and Kurland, L. T., Pathoanatomic changes in amyotrophic lateral sclerosis with special references to the occurrence of neurofibrillary changes, *Arch. Neurol.*, 1962. (In press.)

2 Arnold, A., Edgren, D. C., and Palladino, V. S., Amyotrophic lateral sclerosis; fifty cases observed on Guam, *J. Nerv. & Ment. Dis.*, *117*, 1953, 135-139.

3 Koerner, D. R., Amyotrophic lateral sclerosis on Guam. A clinical study and review of the literature, *Ann. Int. Med.*, 1952, 1204-1220.

4 Kurland, L. T., and Mulder, D. W., Epidemiologic investigations of amyotrophic lateral sclerosis. 1. Preliminary report on geographic distribution with special reference to the Mariana Islands, including clinical and pathologic observations, *Neurology*, *4*, 1954, 355-378, 438-448.

5 Mulder, D. W., and Kurland, L. T., Amyotrophic lateral sclerosis in Micronesia, *Proc. Staff Meet. Mayo Clinic*, *29*, 1954, 666-670.

6 Mulder, D. W., Kurland, L. T., and Iriarte, L. L. G., Neurologic diseases on the island of Guam, *U.S. Armed Forces Med. J.*, *5*, 1954, 1724-1739.

European countries, also Australia and Japan, show that the mortality falls within a narrow range of between 0.7 and 1.0 per 100,000 population; the sex ratio averages about 1.7 males per female.

When we study the prevalence ratio for adults, that for the United States and other countries is about 1/100th of that among the Chamorros of the Marianas and among a large group of Chamorros who have emigrated to California. Thus, on the basis of our earlier studies, it appeared that the high incidence of the disease in the Marianas was limited to the Chamorro population and occurred whether they were residing in the Mariana Islands or elsewhere, such as California.[7] Family studies reported in earlier publications in the United States and other countries revealed that in about 1 out of 15 cases one may expect to find a familial incidence for ALS. Pedigree studies have been compatible with dominant inheritance, although the penetrance appears to be incomplete in many of the families. Pedigree studies on Guam have been inconclusive. There were many difficulties in obtaining accurate family information in this population. Family relationships are often vague, and past family medical histories are frequently incomplete. Furthermore, the civil and church records were destroyed during World War II and there is a stigma associated with this disease since, according to Chamorro folklore, ALS is retribution for sins which the individual or his ancestors may have committed. However, it was clear from earlier studies that for at least 125 years the Chamorros had recognized the disease as occurring in familial aggregates.[8, 9]

At the time of our investigations from 1953 to 1957, we were unable to associate any environmental factor with the disorder and concluded that all of the data collected by us suggested that we were dealing with a disorder of an inherited nature presumably transmitted as a dominant trait with a high degree of penetrance, at least among the Chamorros.

The high gene frequency which such a genetic hypothesis would require could be attained if the gene responsible for the disease was introduced at a time when the population was relatively small. Subsequently, through the effect of drift or some selective survival mechanism, it may have spread to the extent allowing the disease to be recognized as familial even in the early nineteenth century. Either the disease was introduced early in the human history of Guam or after the Spanish colonization, which began about 1667. There is evidence from the writings of the Jesuits who arrived with the first Spanish colonists that the population was healthy and long-lived at that time. During the period 1670 to 1700 the introduction of new infectious diseases into the population, and famine, almost wiped out the Chamorros. It has been suggested that ALS was inadvertently introduced during

7 Torres, J., Iriarte, L. L. G., and Kurland, L. T., Amyotrophic lateral sclerosis among Guamians in California, *Calif. Med., 86* : 6, 1957.

8 Kurland, L. T., and Mulder, D. W., Epidemiologic investigations of amyotrophic lateral sclerosis. 2. Familial aggregations indicative of dominant inheritance, *Neurology, 5,* 1955, 182-196.

9 Kurland, L. T., Epidemilogic investigations of amyotrophic lateral sclerosis. 3. A genetic interpretation of incidence and geographic distribution, *Proc. Staff Meet. Mayo Clinic., 32,* 1957, 449-462.

the period of Spanish colonization and that the repeated epidemics of smallpox from 1700 to 1860 may have resulted in selective survival of those who had inherited the tendency for ALS and perhaps a higher degree of natural immunity at the same time.[10, 11]

Recently, several new developments have influenced our thinking about the possibility of a genetic basis for the disease on Guam. These are: (1) the observation that another neurological disease, referred to as Parkinsonism-Dementia, is also highly prevalent;[12] (2) the study which revealed changes in the collagen of the skin in patients with both neurological diseases;[13] (3) the observations that another disease occurring in familial aggregates, diaphyseal aclasis (multiple exostosis), was highly prevalent in the population;[14] (4) on the island of Saipan cases of ALS among individuals whose mothers were Carolinian and whose fathers were also presumably Carolinian;[15] and (5) a new focus of ALS in an area known as the Kii Peninsula of Japan.[16]

Parkinsonism-Dementia has as its main features an organic type of mental deterioration, a reduced spontaneous motor activity referred to as akinesia, and hyperreflexia. This disease accounts for about 7 percent of adult mortality on the island and has a mean age at onset of about 50 years with a duration of about 3 to 5 years from onset to death. In about one-third of the cases there are pathological changes indicative of upper motor neuron disease and in about 1 out of 6 cases there is also the amyotrophy characteristic of ALS. More careful study has shown that occasionally the ALS cases also show some slight evidence of the Parkinsonism-Dementia features (cerebral and nigral effects). In Parkinsonism-Dementia and to a lesser extent in ALS, one finds a large number of neuronal cells with a neurofibrillary type of degeneration and cells, especially in Sommers Sector, that show signs of granulovacuolar body changes.[17]

For an appreciable proportion of the cases there is a familial history of ALS, Parkinsonism-Dementia Complex, or both. A close relationship between ALS and Parkinsonism-Dementia Complex of the Chamorros is suggested by the similari-

10 Kurland, L. T., and Mulder, D. W., Epidemiologic investigations of amyotrophic lateral sclerosis. 1. Preliminary report on geographic distribution with special reference to the Mariana Islands, including clinical and pathologic observations, *Neurology, 4*, 1954, 355-378, 438-448.

11 Kurland, L. T., *loc. cit.*

12 Hirano, A., Kurland, L. T., Krooth, R. S., and Lessell, S., Parkinsonism-Dementia Complex, an endemic disease on the island of Guam. 1. Clinical features, *Brain*, 1962. (In press.)

13 Fullmer, H. M., Seidler, H. D., Krooth, R. S., Robert, S., Kurland, L. T., and Leonard, T., A cutaneous disorder of connective tissue in amyotrophic lateral sclerosis, *Neurology, 10*, 1960, 717-724.

14 Krooth, R. S., Macklin, M. A. O., and Hilbish, T. F., Diaphysial aclasis (multiple exostoses) on Guam, *Am. J. Human Gen., 13* : 3, 1961, 340.

15 Lessell, S., Hirano, A., Torres, J., and Kurland, L. T., The Parkinsonism-Dementia complex in the Chamorros of the Mariana Islands and California—epidemiologic considerations, 1961. (Unpublished data.)

16 Kimura, K., Kaneko, Z., and Nogi, K., (1961). Epidemiological and geomedical studies on amyotrophic lateral sclerosis and allied diseases in the Kii peninsula (Japan), presented at the Symposium on Geographic Neurology, Sept. 13, 1961, Rome, Italy.

17 Hirano, A., Malamud, N., and Kurland, L. T., Parkinsonism-Dementia Complex, an endemic disease on the island of Guam. 2. Pathologic features, *Brain*, 1962. (In press.)

ties of the age and sex of the cases, by the duration from onset to death, by the histories of the occurrence of one or both of the diseases in siblings or other relatives, and by the pathological and clinical features common to both disorders. There is also an indication that the distribution of the "two" disorders may be similar in the villages of Guam, Rota, and Saipan and that, at least on Rota and Guam, the more remote agricultural communities have a higher incidence of both disorders.[18] It is highly likely that ALS and Parkinsonism-Dementia Complex among the Chamorros are clinical variants of the same disease mechanism. The factors responsible for the spectrum of clinical manifestations are unknown.

The dermal changes are present in many cases of Parkinsonism-Dementia and ALS, both in the Chamorros and among other people in the United States with ALS. The changes include increased mucopolysaccharide, connective tissue disorientation, elastosis, and disorganization of the collagen structure.[19]

The diaphyseal aclasis usually occurs in a familial pattern compatible with dominant inheritance, but as yet there have been no comparative studies of the pathological lesions with those of other cases of multiple exostosis.

At least three and perhaps four cases of ALS have been known to occur among Carolinians on Saipan. Although the possibility remains that parentage may be partly Chamorro, as the number has increased, this explanation has become less tenable and has forced us to reconsider seriously the possibility of an exogenous etiologic factor. This may be nutritional and may have been a part of the Chamorro culture which was adopted in recent decades by the Carolinian immigrants to Saipan.

The possibility exists that the ALS in the Kii Peninsula of Japan is due to a common origin of the Chamorros and the Japanese living in the remote area of the Kii Peninsula. No direct association between these two groups has been established, however, and it is equally plausible that there is some environmental factor common to the two peoples.

Thus, features which stood out as a result of these more recent studies—that Carolinians as well as Chamorros were unduly affected—indicated that environmental factors should be carefully investigated. Also, the association of ALS with dementia and extrapyramidal disease, which has been reported only infrequently before in other populations,[20, 21] raised the question whether there might be a unique mechanism involved in the development of the disease in the Marianas geographic isolate.

The high incidence of neurological disease in the Marianas island population,

18 Lessell, S., Hirano, A., Torres, J., and Kurland, L. T., *loc. cit.*

19 Fullmer, H. M., Seidler, H. D., Krooth, R. S., Robert, S., Kurland, L. T., and Leonard, T., *loc. cit.*

20 Robertson, E. E., Progressive bulbar paralysis showing heredofamilial incidence and intellectual impairment, *A.M.A. Arch. Neurol. & Psychiat.*, *69*, 1953, 197.

21 Van Bogaert, L., and Radermecker, M. A., Scléroses latérales amyotrophiques typiques et paralysies agitantes héréditaires, dans une même famille, avec une forme de passage possible entre les deux affections, *Mschr. Psychiat. Neurol.*, *127*, 1954, 185-203.

with concurrent changes in the structure of the collagen of the skin and the frequent occurrence of multiple exostosis, suggested to us that there might be a toxic factor, perhaps one similar to the aminonitrile-like compounds responsible for human and experimental lathyrism. It has been shown that appropriately selected lathyrogenic agents fed to appropriate species of animals at specific ages produce neurological disease, multiple exostoses, and changes in collagen. Although Krooth *et al.*[22] state that the multiple exostoses of Guam differ in site from those observed in the odoratism of experimental animals, this problem appears to be worth further exploration.

According to studies by Whiting,[23] a nutritionist who participated in some of the earlier projects on Guam and Saipan, the Chamorros learned, perhaps centuries ago, to treat a local starch-containing nut which is known to contain a highly toxic material. When the nuts are treated through ritual washing procedure, most, if not all, of the water-soluble toxic compounds are removed.

Our working hypothesis at this time is that there may be an inherent relative inability to detoxify some of a residual toxic compound to which this population is exposed. Presumably by interfering with the hepatic production of essential enzymes, such an agent could conceivably lead to neuronal damage, collagen disorganization, or, in the young, multiple exostosis. Gout and diabetes may also be unduly prevalent among the Chamorros and perhaps also fit into this pattern.

Animal studies to test this hypothesis are under way in several laboratories. Needless to say, elucidation of this mechanism on Guam could clarify the problems of ALS, presenile dementia, and perhaps some forms of Parkinsonism in other countries as well. It is conceivable that genetic predisposition is, after all, important and exists perhaps in the form of a limited capacity to detoxify agents which may be present in very small quantities in certain foods. Obviously, until a specific agent can be identified, the genetic hypothesis which was supported by an extensive amount of data in the earlier studies continues as one of the reasonable explanations for this unusual population focus of chronic disease.

NEEL: Dr. Kurland has confronted us with an intriguing situation. It is by no means clear whether the high morbidity rate in the isolate described by him is in any way due to its population structure. It is equally possible that exogenous factors are largely responsible for the neurological disorders from which this community suffers.

Dr. Klein will now discuss briefly another isolate in which chronic disease is common.

KLEIN: Although Geneva is an international city, there exists in its surroundings a small Savoyard village which has all the qualities of an isolate. In this village, with about 300 inhabitants and a consanguinity rate of about 8 percent, we

22 *Loc. cit.*
23 Whiting, M. G., Personal communication.

found several hereditary affectations of recessive type: alkaptonuria, phenylpyruvic idiocy, congenital cataract; all these cases could be traced to a common ancestor;[1] moreover, there were cases of idiopathic tetany, Friedreich's ataxia, and mental defect. This fact shows that such isolates may include in their gene pool 6 to 8 recessive genes in latency which suddenly manifest themselves in about the same generation.

From 1688 to 1749, the total consanguinity rate in this village was 4.55 percent; from 1750 to 1799, 8.16 percent; from 1800 to 1849, 12.62 percent; from 1850 to 1899, 14.35 percent; and from 1900 to 1960, 7.51 percent.

A full account of the demographic and genetic aspects of this isolate will be published elsewhere.[2]

NEEL: Dr. Fraser's comments will also deal with deleterious gene concentration in isolates.

FRASER: I intend to discuss several aspects of inherited defects in isolates.

First I want to report briefly on a series of isolates, each of which has a high incidence of a particular type of hereditary defect. These isolates exist on an island off the coast of Yugoslavia, called Krk or Veglia. Its inhabitants number about 17,000. This island is well known to geneticists and, among others, Hanhart[1] has studied one of the isolates which I shall describe.

There are on this island about 40 villages of uniform size, each with a population of about 400. For various economic reasons, marriage partners usually belong to the same village and endogamous marriages of this type have prevailed for some centuries. It is rather striking that on this island, which I was able to observe only perfunctorily with some Yugoslav colleagues, three of these villages (and probably a fourth) have their own brand of recessive disease. Perhaps the most striking of these is the village of Baska, where a unique type of pituitary dwarfism is common. It is possible that this pathological entity may not occur elsewhere, although Hanhart thinks he has seen it in certain valleys in Switzerland. In each case the disease occurs in several sibships, and attempts have been made to construct pedigrees, although the information is rather scanty.

Both males and females are completely infertile. These unfortunate dwarfs were called marine cretins[2] because goiter is endemic on this island, and for many centuries all pathological curiosities occurring in areas of endemic goiter have been labeled as cretinism. In fact, these people are far from being cretinous. They are very shrewd businessmen and among the richest persons on the island.

1 Bable, J., Bamatter, F., Courvoisier, A., Franceschetti, A., Klein, D., and Lapine, A., Troubles familiaux du métabolisme des acides aminés (alcaptonurie, oligophrénie phenylpyruvique, cataracte, congénitale dans une même famille). *Schweiz. Med. Wschr., 90,* 1960, 863-866.

2 Dodinval, P., and Klein, D., Caractères génétiques et démographiques d'un petit village savoyard, Proceedings, Second International Conference on Human Genetics, Rome. To be published in *J. Génét. Hum.* (Geneva), *11* : 1, 1962.

1 Hanhart, E., Zur Mendelistischen Auswertung einer 33 Jahre langen Erforschung von Isolaten, *Novant'anni delle Leggi Mendeliane,* Ed. L. Gedda, Rome, 1955, pp. 397 ff.

2 Von Jauregg, W., Über Marinen Kretinismus, *Wiener Klin. Wschr., 19,* 1906, 1272 ff.

In another village an unusual type of spastic paraplegia occurs in several sibships. A third village shows a considerable rate of affliction with total albinism. The fourth village, which unfortunately I was not able to visit, has a high incidence of myoclonic epilepsy and, I understand, some forms of this disease are inherited in a recessive manner. Goiter and schizophrenia are also very common on this island.

The second problem to which I would like to draw attention concerns the variety of recessive genes which may exist in an isolate. My own studies on deaf-mutism in England have a bearing on this question. I have seen about 3000 so-called

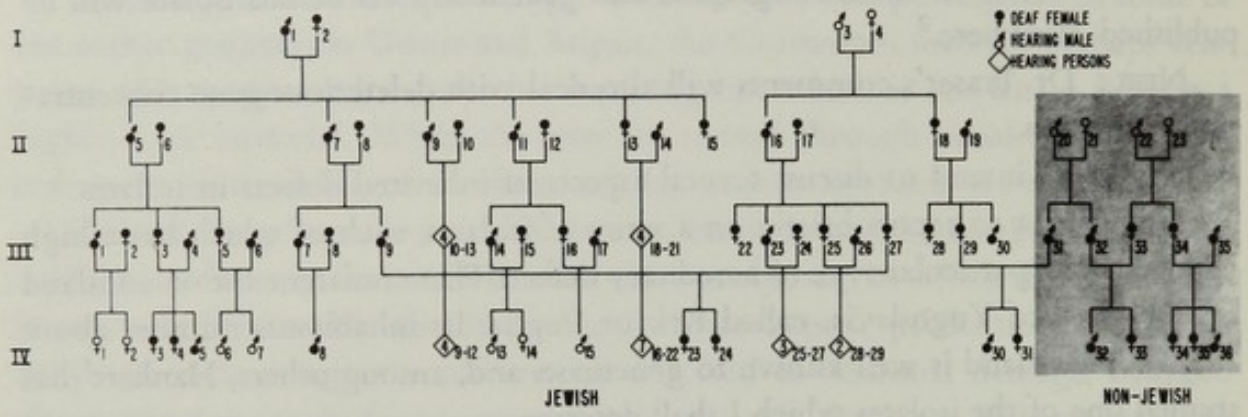


FIG. 40. Congenital deafness in a Jewish family.

deaf-mutes, and most of these suffer from congenital deafness. I have been able to distinguish some twenty different causes of deafness in childhood. Among these are five clinically definable recessive conditions, and no doubt there are others. This leads to the phenomenon that, in an outbreeding community such as the population of England, matings between people suffering from recessive deafness do not often result in deaf children. One does see recessive deafness in two generations where both parents are deaf but very rarely in three. I understand from Dr. Morton that in some areas of Japan the situation is different. The situation is also different in the only large isolate I have been able to find in England, which is the Jewish population. In this population, where there are perhaps four or five hundred congenitally deaf people, there is a very large pedigree in which deafness may be traced for four generations (Fig. 40). Nevertheless, there is no indication of dominant inheritance.

A series of marriages between members of this family and unrelated deaf persons have resulted in deaf children. In other cases the children were hearing.

Since the matings between unrelated homozygotes result so frequently in affected children, it must be concluded that a particular recessive gene for congenital deafness is rather widespread in the Jewish community. This gene appears to exist in both Ashkenazic and Sephardic Jews. In the few intermarriages between deaf Jewish persons and deaf non-Jews, there have been no deaf children except in one case, where a member of this pedigree married a man whose mother was Italian and whose father was English without any recorded Jewish ancestry. He

was also evidently suffering from recessive congenital deafness. Both children in this case were deaf, and his brother married an English deaf person also suffering from recessive deafness, and their children were deaf. So presumably this gene is widespread in Ashkenazic and Sephardic Jews and also occurs in non-Jews, at any rate in Britain and in Italy. It is unfortunately not one of the clinically identifiable genes, and it is not the only gene for congenital deafness in the Jewish community, since hearing children have resulted from matings between deaf members of this family and unrelated Jewish persons suffering from recessive congenital deafness.

I have also found the syndrome of deafness with retinitis pigmentosa among English Jews. There exist, therefore, at least three different genes that cause recessive congenital deafness in this large isolate.

NEEL: Dr. Siniscalco will add some remarks on the unusual concentrations of certain genotypes in some Sardinian isolates.

SINISCALCO: Night blindness of the dominant type appears to be a very rare condition. However, in a certain village in Sardinia we found this abnormality to be quite common. In fact, about 4 percent of the population are affected. So far as we could make out from the available historical records, this defect has existed in this isolate for 400 years or longer. The mode of transmission is certainly dominant, and we have reason to assume that the dominance may be of the incomplete type. In one of the families observed by us, both parents were night-blind and there had been several miscarriages. It is therefore possible that the gene for dominant night blindness may be lethal in the homozygous condition. The situation in this family is, however, complicated by the fact that there was also ABO incompatibility.

This population comprises only about 2000 individuals, and 7 percent of the marriages are between first cousins. Since this community is not only isolated but also socially stratified, we were able to calculate that the subpopulation from which a person chooses his partner numbers only about 84 individuals. It is therefore possible that only a few genes for night blindness were originally introduced into this village and that their relative increase may be due to the peculiar population structure.

The same type of night blindness is also found in many other villages of Sardinia. The local ophthalmologists tend to ascribe all these scattered cases to migration from the one village in which the concentration of this defect is very high, but there is not enough evidence in favor of this theory.

Since Dr. Sheba is interested in the possible affinities of Sardinians and some of the Jewish communities to the ancient Phoenicians, it would be interesting to look for this type of night blindness in Israel.

In another isolate in the southern part of Sardinia we found a high frequency of another ocular defect—namely, congenital myopia. This, by the way, is the area in which the Phoenicians are believed to have been settled.

I would like to take this opportunity to direct attention to the unusual possibilities offered by small inbred populations for autosomal linkage studies. It is well known that autosomal linkage, unless very close, is difficult to detect. But when

two populations which have attained different equilibrium levels for two linked autosomal genes meet and intermarry, the linkage will give rise to association between certain phenotypes for a few generations following the outbreeding.

This was the method that enabled us to indicate linkage between thalassemia and the Lewis system. The likelihood for linkage was significant at the 1-percent level, although the recombination frequency was as high as 17 percent in our material. Similar opportunities for linkage studies must exist in Israel at the present moment, when many small groups with different gene frequencies are beginning to coalesce.

HIRSCHHORN: I shall report briefly on another case in which a mutant gene attained a high concentration in a small isolated population. We have studied a rather large family[1] settled now in the United States but deriving from two small mountain villages in Italy. Among the members of this family we found a very high incidence of a type of hypercholesterolemia which, in the homozygous state, is lethal to males in their thirties. With the aid of Dr. Siniscalco we collected data from the two home villages in Italy from which these individuals originated. Consanguineous matings had been frequent during several generations preceding the immigration of the group to the United States and were continued in the new country.

However, in the mountain villages it was impossible to pick out the hypercholesterolemia, which is now becoming manifest in the new environment. It appears that in isolates certain genes may accumulate in latency. Any sudden change in the environment will cause these genes to become penetrant and exhibit their effect in the phenotype. This may apply to diabetes and other chronic disorders discussed at a previous session.

NEEL: Thank you. The next speaker will be Dr. Lehmann. He will also discuss some "latent" genetic defects which remain hidden in certain populations and are revealed by very unusual environmental conditions.

LEHMANN: Recent progress in pharmacology has focused attention on a series of inherited biochemical defects which had previously been inconspicuous or unknown. Porphyria, for example, can be considered harmless unless the affected carriers are given barbiturates. Because of the introduction of barbiturates, many people now have dangerous episodes. A similar situation exists for the gene that gives rise to deficiency of the enzyme pseudocholinesterase.

Cholinesterase—an enzyme hydrolyzing acetylcholine—was discovered by Dale, and its importance lies in the role it plays in the transmission of neural excitation. During World War II it was found that human blood contains two enzymes capable of hydrolyzing acetylcholine. The first exists in the red cells and is the same enzyme which has an important function in the nerve-muscle endings. The second is contained in the plasma and is not a true acetylcholinesterase. It

[1] Hirschhorn, K., and Wilkinson, C. F., Jr., The mode of inheritance in essential familial hypercholesterolemia, *Am. J. Med.*, *26*, 1959, 60-67.

certainly does not hydrolyze acetylcholine at physiological concentrations. For this reason it was named pseudocholinesterase.

Pseudocholinesterase is present in many organs besides the plasma. Apparently the plasma enzyme is made entirely in the liver and hence, when the liver is below par, the plasma enzyme level falls. This fact has been used for the clinical assessment of liver function. When suxamethonium was introduced by the anesthetists as a short-acting muscle relaxant, it was found to provoke in certain subjects a very prolonged apnoea. It turned out that in normal persons suxamethonium is rapidly destroyed by the plasma pseudocholinesterase and that this destruction accounts for its characteristic short action. In persons developing apnoea upon administration of the drug, the pseudocholinesterase level is low and the action of suxamethonium is therefore prolonged. Later it became clear that a low level of plasma pseudocholinesterase occurs not only in persons with liver damage but in certain otherwise completely normal individuals. In the latter, the low enzyme level appeared to be familial.

Kalow and his colleagues have shown that the enzyme found in these rare individuals differs from the usual type in two respects: it is less effective against a wide range of substrates and more resistant to most inhibitors. Kalow and Genest[1] devised a system using 5×10 M benzoylcholine as a substrate and a 10 M concentration of the local anesthetic dibucaine ("Nupercaine") as an inhibitor. Under these conditions, dibucaine inhibits the normal enzyme by about 80 percent, whereas the atypical enzyme is inhibited by about 20 percent. There is also an intermediate type of subject whose sera are inhibited by about 50 percent. This intermediate type is more common than the extreme abnormal type and in some populations constitutes about 3 percent.

The percentage inhibition produced by dibucaine in the set-up of Kalow and Genest is usually called the dibucaine number. Genetic studies indicate that the three categories are determined by two allelic genes: the homozygotes for the usual and atypical genes have dibucaine numbers of about 80 and 20 respectively, whereas the heterozygote, presumably possessing a mixture of both enzymes, has an intermediate value. In the majority of families investigated, the results support this theory.

Harris *et al.*,[2] using sodium fluoride as a differential inhibitor and comparing the fluoride and dibucaine numbers, have shown that there is a further variant of the normal enzyme with an increased resistance to this inhibitor.

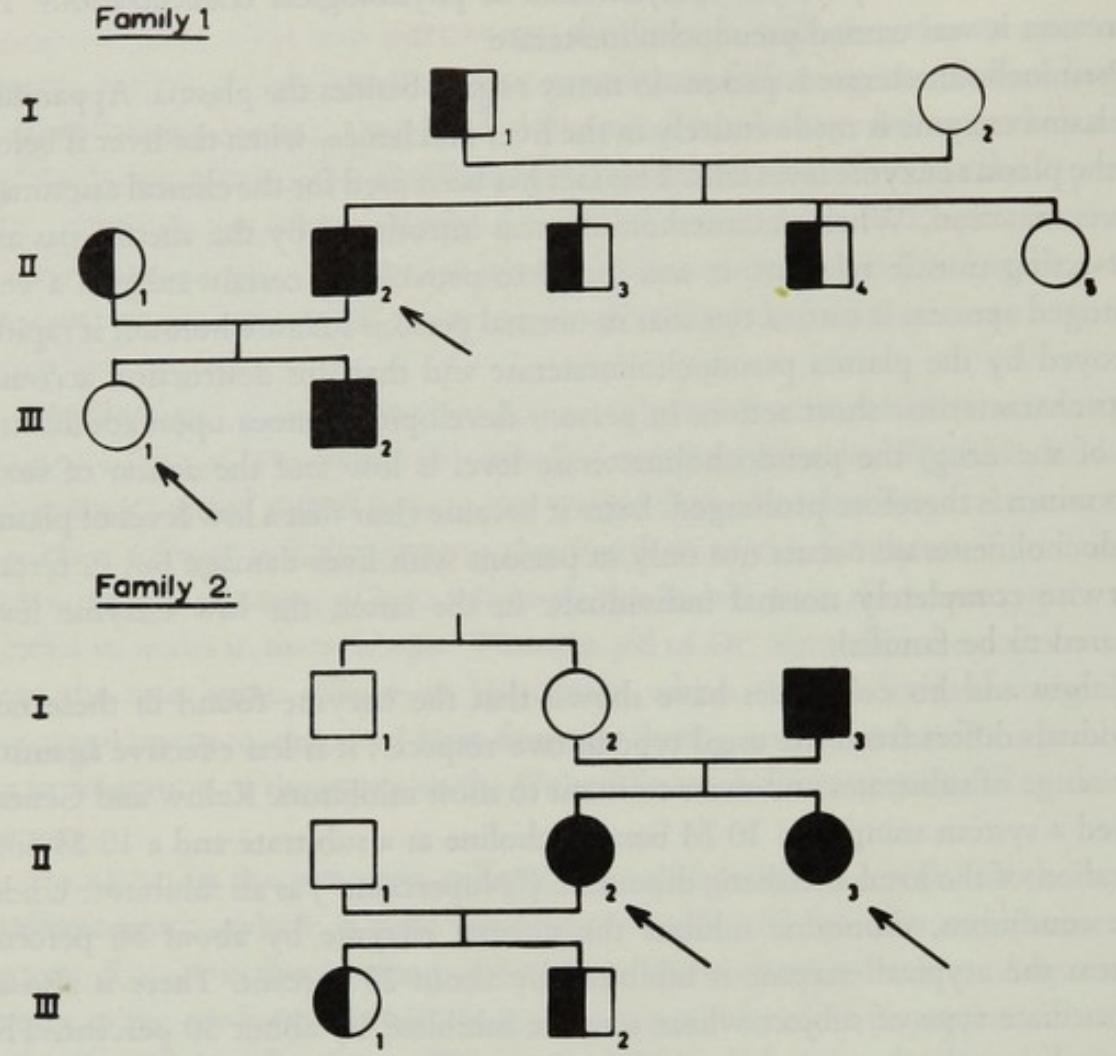
Two families have been reported[3,4] in which the dibucaine results cannot be

1 Kalow, W., and Genest, K., A method for the detection of atypical forms of human serum cholinesterase, *Canad. J. Biochem. Physiol., 35,* 1957, 339 ff.

2 Harris, H., Whittaker, M., Lehmann, H., and Silk, E., The pseudocholinesterase variants. Esterase levels and dibucaine numbers in families selected through suxamethonium-sensitive individuals, *Acta genet., 10,* 1960, 1 ff.

3 *Ibid.*

4 Kalow, W., and Staron, N., On the distribution and inheritance of atypical forms of human serum cholinesterase as indicated by dibucaine numbers, *Canad. J. Biochem. Physiol., 35,* 1957, 1305 ff.



● Abnormal dibucaine number (presumed abnormal homozygote).

◐ Intermediate dibucaine number (presumed heterozygote).

○ Usual dibucaine number (presumed normal homozygote).

↖ Anomalous phenotypes.

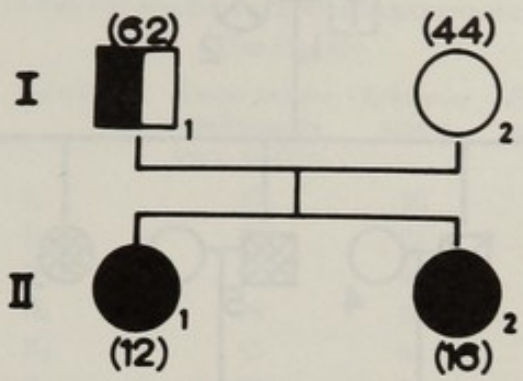
FIG. 41. Two families in which the inheritance of pseudocholinesterase deficiency cannot be explained on the assumption of one mutant and one normal allele.

explained on the theory of two allelic genes. These are shown in Figure 41. In both cases the anomalous individuals are classified by the dibucaine technique as atypical homozygotes, whereas the pedigree data suggest that they are heterozygous. Dr. J. Liddell, Mrs. E. Silk, and I have now seen a third such family, which is described in Figure 42 and Table I. In this family two sisters (II_1 and II_2) have dibucaine numbers characteristic of the atypical homozygote, and their parents (I_1 and I_2) appear to be a heterozygote and a normal homozygote respectively.

In order to explain this type of discrepancy, Kalow and Staron[5, 6] have sugges-

5 *Ibid.*

6 Lehmann, H., Silk, E., and Liddell, J., Pseudo-cholinesterase, *Brit. Med. Bull., 17,* 1961, 230-233.



● Abnormal dibucaine number (presumed abnormal homozygote).

◐ Intermediate dibucaine number (presumed heterozygote).

○ Normal dibucaine number (presumed normal homozygote).

Figures in brackets show enzyme levels.

FIG. 42. Another family with unusual mode of inheritance of pseudocholinesterase deficiency.

TABLE I

ONE FAMILY WITH AN UNUSUAL MODE OF INHERITANCE OF ATYPICAL PSEUDOCHOLINESTERASE

(See Fig. 42)

Individual	*Serum pseudo-cholinesterase level, units/ml.*	*Dibucaine number*	*Fluoride number*
I_1	62	65	56
I_2	44	76	64
II_1	12	21	24
II_2 (Propositus)	16	21	22

ted that there are several allelic genes which may govern the synthesis of the normal pseudocholinesterase, each determining its production at a different rate. The extreme of such a series would be an allele producing an absence of pseudocholinesterase activity. The mode of inheritance in our family (Fig. 42) would be explained if the mother (II_2) was actually a heterozygote for this "silent" gene and a normal allele. This is supported by the fact that her pseudocholinesterase level of 44 units/ml. is well below the normal range of 65-125 units/ml. The father is heterozygous for one dose of the gene determining the production of the *atypical* esterase. Both children would then be heterozygous for the atypical and the "silent" genes, and their dibucaine numbers would be those of the atypical homozygote. It should be noted that the combination of a normal and a "silent" gene does not always result in abnormally low enzyme levels. This is another case of variable dominance relationships between two alleles such as seen in hemopihlia

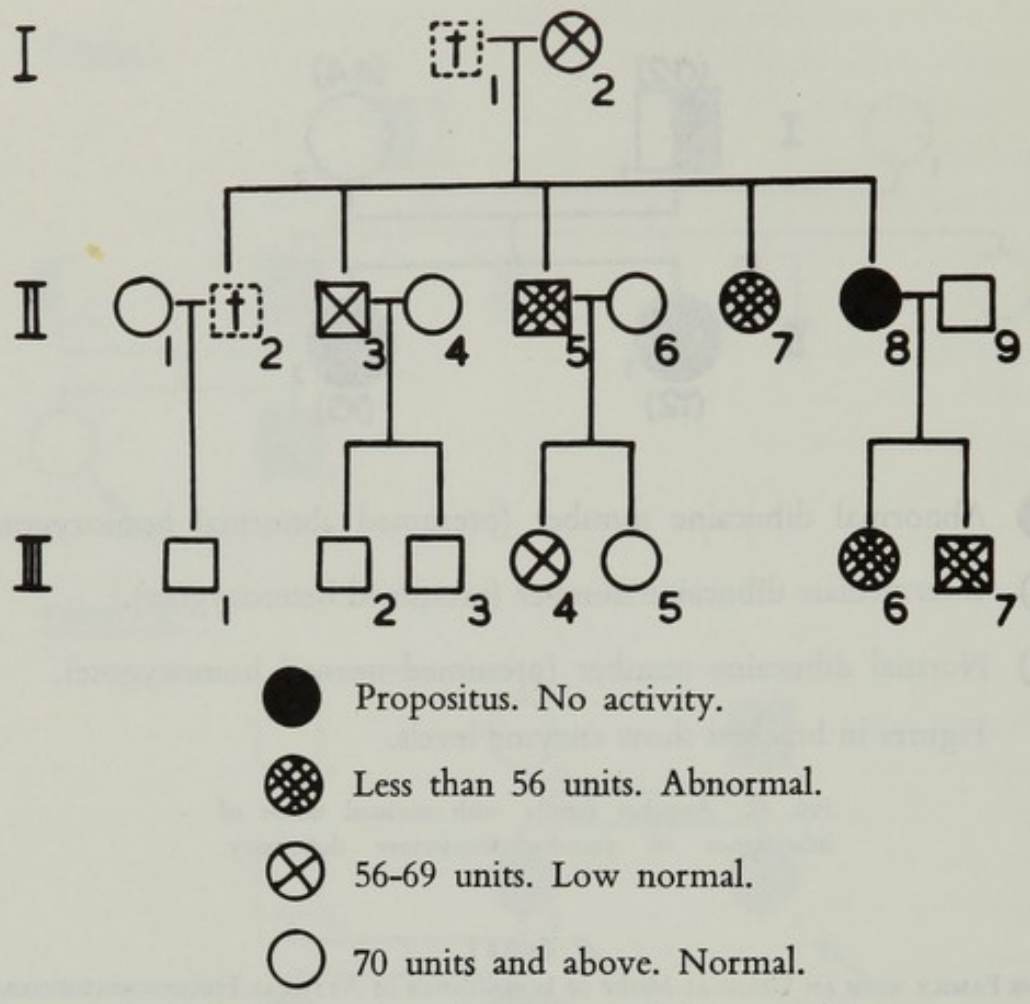


FIG. 43. Pedigree of a family in which one member was completely devoid of pseudocholinesterase activity.

and Glucose-6-Phosphate-Dehydrogenase deficiency, when on occasion one gene appears to perform almost the work of two.

A serious objection to this theory has been that it predicts the existence of homozygotes for the "silent" gene. These should lack all pseudocholinesterase activity in their sera. Until quite recently such individuals had not been described. We have now seen such a person, a Greek woman aged 42, who was brought to our attention because she developed a prolonged apnoea following the administration of suxamethonium. No pathological cause could be found for this complete absence of pseudocholinesterase activity, which has persisted during the four months she has been under observation. The true cholinesterase level of the red cells was 97 units/ml., a normal value. The study of the family summarized in Figure 43 and Table II suggests that this deficiency is inherited. Two children and two siblings have subnormal pseudocholinesterase levels and are probably heterozygous. The mother, one other sibling, and one niece have values which are just within the normal range. These individuals may also be heterozygous. All these carriers of both the normal and the "silent" gene had normal dibucaine and fluoride numbers. The serum of the propositus with complete lack of pseudocholinesterase activity did not affect the dibucaine numbers of sera from normal and atypical homozygotes when mixed with them *in vitro*.

TABLE II
THE FAMILY OF THE PROPOSITUS LACKING PSEUDOCHOLINESTERASE ACTIVITY
(See Fig. 43)

Individual	*Serum pseudo-cholinesterase level, units/ml.*	*Dibucaine number*	*Fluoride number*
I_2	67	80	64
II_1	78	81	67
II_3	66	82	64
II_4	78	80	63
II_5	53	83	67
II_6	70	80	65
II_7	55	78	64
II_8 (Propositus)	Nil	—	—
II_9	78	78	64
III_1	74	81	63
III_2	112	80	68
III_3	84	78	62
III_4	67	80	64
III_5	98	81	61
III_6	52	82	64
III_7	55	82	65

These studies indicate the existence of a number of pseudocholinesterase variants. An additional possible variant, where the pseudocholinesterase activity was like that seen in atypical homozygotes but the dibucaine number was somewhat higher than usual, has been described in several members of another family. The position is not unlike that found for human hemoglobins, and the "silent" pseudocholinesterase gene presents a problem similar to that of thalassemia. Some authors consider that in thalassemia normal hemoglobin production is reduced, and others envisage that the normal pigment is replaced by an abnormal hemoglobin which cannot be recognized by present laboratory procedures.[7] Either of the two explanations could also be applied to the inheritance of the "silent" pseudocholinesterase gene. It may be of particular interest to the participants at this conference that the individuals in whom the rare variants were discovered appeared to be often of Mediterranean ancestry. Of the families with the "silent" pseudocholinesterase gene, at least two, one described in Figure 42 and one described in Fig. 43, are wholly or partially of Mediterranean origin.

Here, then, is yet another class of apparently innocuous biochemical deviations which may well gain significance in the characterization of population groups or even of isolates. It has already been pointed out by Dr. Cabannes (see p. 62) that the rarer hemoglobin variants appear quite often to be restricted to certain well-defined geographic areas. Thus, hemoglobin L has been found exclusively in several dozen families in India. Hemoglobin J may also be restricted to Aryan Indians. Hemoglobin K, with one exception in Bengal, has been found only in

7 *Ibid.*

Dravidian Indians. Hemoglobin Lepore may well be peculiar to Mediterranean peoples, for the Hb Lepore recently reported from the Papuan area has since been proved to differ from the Lepore described in Mediterraneans.

Biochemical characteristics that leave viability comparatively unimpaired, at least in the heterozygote, may be as informative in the study of isolates as the serious afflictions described by several previous speakers at this meeting.

NEEL: Thank you, Dr. Lehmann. Dr. Lehmann has stressed the potential significance of innocuous biochemical errors in the analysis of isolate structures. Dr. Singer will now deal with the information that may be derived from broad anthropological screening surveys regarding the differentiation and divergence of certain African isolates. He will show that biochemical anthropology may often refute the earlier hypotheses that have been advanced on the sole basis of physical anthropology.

SINGER: I wish to add some comments concerning the results of isolation in populations which probably moved apart in the past and then came together again at a later date. The phenomena I shall describe may be relevant to the present-day population of Israel.

In Southern Africa we have a fine opportunity for studying apparently indigenous populations, two of which are very well known to you—namely, the Hottentots and the Bushmen. Numerous anthropologists have considered these two groups to constitute a major division separate from the rest of the population of Africa. Thus they have been considered physically and culturally distinct from the Negroids and have been given various connotations including the "Yellow-skinned peoples," and even the "Mongoloids."

Some of our research during the past 6 years has provided information indicating the probable origins of these racial groups. The Nama-speaking Hottentots are physically quite different from the other populations of Africa, especially the Bantu-speaking Negroids of Southern Africa. The Negroids are black or near-black, possessing long, prognathous faces, long (dolichocranic) heads, crinkly or fuzzy hair, broad noses, and thick lips. On the other hand, the Hottentots that were studied have a range of skin color from yellow to dark brown and possess flat (orthognathous), long faces characterized by broad, prominent cheek bones, and usually tend to be distinct from the Negroids, by whom they now are surrounded geographically. The Bantu-speaking Negroids are generally settled agriculturalists and herders of cattle and goats, with endogamous marriage systems and a tribal culture and language clearly distinguishable from those of the exogamous nomadic Hottentots. Nevertheless, some of the Bantu language forms contain elements of the Hottentot clicks.

Our recent serological studies[1] on the Nama-speaking Hottentots demonstrate

1 Singer, R., Weiner, J. S., and Zoutendyk, A., The blood groups and origins of the Hottentots, Proceedings, Second International Conference on Human Genetics, Rome, 1961. (In press.)

decisively that the Hottentot is essentially an African Negroid with a long history of differentiation in the southern part of Africa. The blood groups show no affinities with either Caucasoids or Mongoloids. A very high frequency of group B and a complete absence of Rh negatives are distinctive features of our series. As regards cDe, V, Js, and Henshaw, the frequencies in the Hottentots are in close correspondence with those characteristic of Bantu-speaking Negroids. Furthermore, the reaction to the C^N antigen (Sturgeon's Negro Variant) is identical with that of the Bantu, whose reaction differs pronouncedly from that of Whites, Indians, and Cape Coloreds (Mulattoes) in South Africa.

Thus, on the one hand our data indicate an obvious divergence in physical features, whereas, on the other hand, there is a distinctly close affinity in the serological pictures of the Hottentots and the Bantu-speaking Negroids.

We believe that the Hottentots, Bushmen, and Bantu-speaking Negroids originated from a common ancestral stock, then separated off and, by isolating mechanisms, developed into three micro-evolutionary units, which, in historic times at any rate, may have intermixed to varying degrees and certainly at present are integrating slowly.

Another group we are studying, in a sense a control group, are the Rehoboth Basters of Southwest Africa. ("Baster" is a derivation of the English word "bastard," but in Afrikaans it means "mixed" rather than "illegitimate.") This population of approximately 10,000 people derives almost entirely from intermarriages during the past 90 years between Hottentots and Caucasoids of Dutch, German, or English extraction. In many families the interethnic union was followed by a period of inbreeding. In 1908 the German anthropologist Fischer, employing anthropometric methods, studied a sample of this population and also recorded detailed genealogies of the subjects examined. His results, published in 1913,[2] constitute the first detailed description of human "hybridization." We are now studying the offspring of the people investigated by him, attempting to complete the pedigrees over many generations and to assess the effects of inbreeding continued for at least two generations in a partially isolated population.

NEEL: The last discussant at this meeting will be Dr. Walter Burdette, who will briefly describe the Mormon isolate and the well-recorded information regarding the genetic relationship of this community to other population groups.

BURDETTE: In connection with the discussion this morning, I should like to draw attention to a United States population isolate of unique interest. The Mormons, or members of the Church of Jesus Christ of the Latter-day Saints, originated chiefly in Western Europe and migrated into the western intermountain region of the United States more than one hundred years ago; they now constitute a rather stable group in the population, available for genetic study. The advantages

2 Fischer, E., *Die Rehobother Bastards und das Bastardierungsproblem beim Menschen*, Jena, Fischer, 1913.

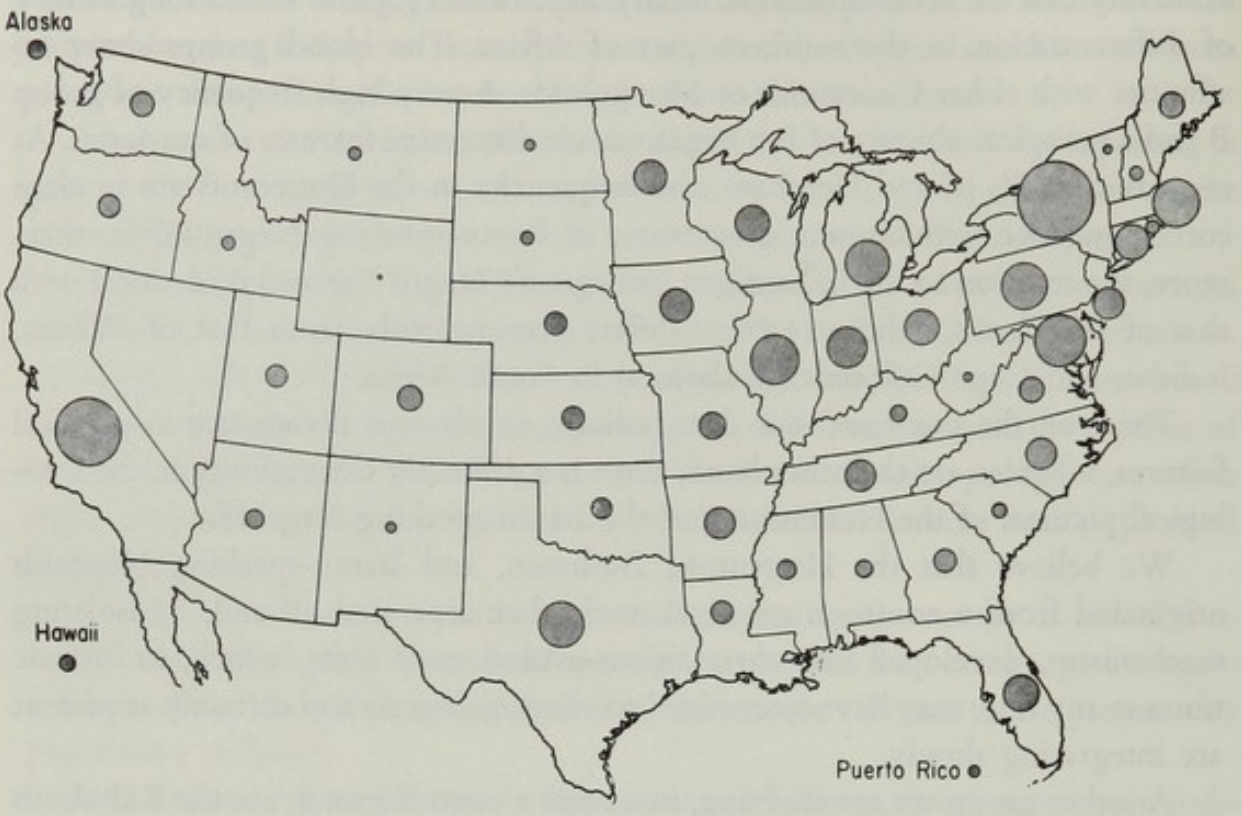


FIG. 44. Distribution of geneticists in the United States.

TABLE I

MICROFILMS OF GENEALOGICAL ASSOCIATION

United States	66 926*	Canada	5 196
Sweden	54 344	France	4 975
Denmark	36 713	New Zealand	1 038
Great Britain	32 809	Switzerland	980
Netherlands	26 723	Hungary	927
Mexico	26 328	Iceland	763
Germany	19 190	Bahamas	608
Finland	13 318	Australia	605
Belgium	6 458	Italy	72
Norway	6 301	Miscellaneous	807

Total: 444,761,000 pages 1,482,538 volumes 305,081* microfilms

* Rolls (100 feet each).

of genetic studies in this community are several. Plural marriages were not uncommon two generations ago, and it is not unusual to encounter an individual with an exceedingly large number of cousins living in geographic proximity. However, these marriages were very rarely consanguineous. Marriages still occur at a relatively early age, and families tend to be large by Western standards.

Because of certain ordinances and beliefs of the church, including vicarious baptism, careful genealogic records are constantly being compiled. Currently there are 22 million names on file in the Genealogical Society of this church. In

addition, individual members are encouraged to construct carefully documented pedigrees, and sometimes it is gratifying to find that accurate genetic records are already available when medical genetic studies are conducted. Salt Lake City is possibly the only place where paraphernalia for genealogies are commonly sold in department stores. Land records, wills, vital statistics, church records, Bibles, and tombstone records have been collected from many countries, ranging from Europe to Polynesia. The prodigious extent of this collection may be surmised from the microfilm available (Table I). So far as records of Jewish populations are concerned, there are about 30,000 pages of records in these archives from synagogues in and about London. Much of the information will be placed on punch cards and tapes in the near future.

We are currently coding the medical records of the University of Utah so that they may be linked to those in the Genealogical Society. The inheritance of susceptibility to a number of conditions—including several types of muscular dystrophy and deafness; carcinoma of the breast, stomach, bowel, and prostate; choroidermia, multiple epidermal inclusion cysts; and osteomas—has been assessed by the staff of the University of Utah,[1-21] utilizing these two sources of information. The number of collaterals, when one is studying a specific inherited trait in this population, is advantageously large.

The present audience may also be interested in the number and distribution of a quite different type of population in the United States, that of the geneticists themselves (Fig. 44). There are 2195 scientists currently engaged in projects related to genetics; and their names and addresses have been compiled, geographically and

1 Gardner, E. J., A genetic and clinical study of intestinal polyposis, a predisposing factor for carcinoma of the colon and rectum, *Am. J. Human Gen., 3,* 1951, 167-176.
2 Gardner, E. J., and Richards, R. C., Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis, *Am. J. Human Gen., 5,* 1953, 139-147.
3 Gardner, E. J., and Stephens, F. E., Breast cancer in one family group, *Am. J. Human Gen., 2,* 1950, 30-40.
4 Gardner, E. J., and Stephens, F. E., Cancer of the lower digestive tract in one family group, *Am. J. Human Gen., 2,* 1950, 41-48.
5 Gardner, E. J., and Woolf, C. M., Intestinal polyposis and carcinoma originating from a mutation in a family group, *Cancer, 5,* 1952, 695-699.
6 Gardner, E. J., Woolf, C. M., and Shaffer, J. O., The inheritance of cancer involving different areas of the human gastrointestinal tract, *Proc. 2d Nat. Cancer Conf., 1,* 1952, 847-855.
7 Gardner, J. E., Mendelian pattern of dominant inheritance for a syndrome including intestinal polyposis, osteomas, fibromas, and sebaceous cysts in a human family group, *Novant'anni Delle Leggi Mendeliane, 27,* 1955, 321-329.
8 Perkoff, G. T., Nugent, C. A., Jr., Dolowitz, D. A., Stephens, F. E., Carnes, W. H., and Tyler, F. H., A follow-up study of hereditary chronic nephritis, *A.M.A. Arch. Int. Med., 102,* 1958, 733-746.
9 Plenk, H. P., and Gardner, E. J., Osteomatosis (Leontiasis Ossea). Hereditary disease of membraneous bone formation associated in one family with polyposis of the colon, *Radiology, 62,* 1954, 830-840.
10 Spear, D., and Stephens, F. E., Choroideremia, its inheritance in a family (1), *Trans. Pacific Coast Oto-Oph. Soc., 33,* 1953, 215-228.
11 Stephens, F. E., Heredity counseling. Muscular dystrophy and cancer, *Eug. Quart., 1,* 1954, 261-263.
12 Stephens, F. E., Hereditary multiple sebaceous cysts, *J. Hered., 1,* 1959, 299-301.
13 Stephens, F. E., Sampling techniques available in human genetics, *Am. J. Human Gen., 6,* 1954, 60-65.
14 Stephens, F. E., and Dolowitz, D. A., Hereditary nerve deafness, *Am. J. Human Gen., 1,* 1949, 37-51.
15 Stephens, F. E., Gardner, E. J., and Woolf, C. M., A recheck of Kindred 107, which has shown a high frequency of breast cancer, *Cancer, 11,* 1958, 967-972.

alphabetically, in a recent publication sponsored by the Genetics Study Section, Division of Research Grants, National Institutes of Health.[22] In the interest of facilitating communication, I should hope that a similar list will be forthcoming from the Mediterranean area as one function of the organization proposed by Dr. Sheba and that we will have no isolates among populations of geneticists.

NEEL: Dr. Burdette has given this session a most pleasant closing. In any case, the hour is hardly ripe for a summary of the more theoretical issues that have occupied us, since the next session will illuminate the same problems from a different angle.

16 Stephens, F. E., Perkoff, G. T., Dolowitz, D. A., and Tyler, F. H., Partially sex-linked dominant inheritance of interstitial pyelonephritis, *Am. J. Human Gen., 3,* 1951, 303-313.
17 Woolf, C. M., A genetic study of carcinoma of the large intestine, *Am. J. Human Gen., 10,* 1958, 42-47.
18 Woolf, C. M., A further study on the familial aspects of carcinoma of the stomach, *Am. J. Human Gen., 8,* 1956, 102-109.
19 Woolf, C. M., An investigation of the familial aspects of carcinoma of the prostate, *Cancer, 13,* 1960, 739-744.
20 Woolf, C. M., and Gardner, E. J., Carcinoma of the Gastrointestinal tract, *J. Hered.,* 41, 1950, 273-276.
21 Woolf, C. M., and Gardner, E. J., The familial distribution of breast cancer in a Utah kindred, *Cancer, 4,* 1951, 515-520.
22 *Directory of Geneticists in the United States,* Genetics Study Section, Division of Research Grants, National Institutes of Health, U.S. Public Health Service, Department of Health, Education, and Welfare, 1960.

SESSION 5 C. STERN, *Chairman*

THE CONCENTRATION OF RARE GENES IN THE PAST AND IN MODERN TIMES

STERN: The first speaker of our rather extensive program today is Dr. Böök.

JAN A. BÖÖK

Recent Work in Genetic Epidemiology in Sweden

In these days of biochemical genetics and clinical cytogenetics, the results of epidemiological investigations of genetic diseases may seem fairly modest. Nonetheless, such investigations, which require a well-developed clinical and genetic skill, constitute the framework of medical genetics. It is not a field where either new or experienced investigators collect easy, sensational results. On the other hand, I believe that the observations may be more reliable. There is no reason to elaborate this point in this group of esteemed colleagues and experts. Let it suffice to say that there will always be a need for new and extended studies of all the factors that influence the behavior of genes with pathological effects in human populations.

In the past there has been—in Sweden—much emphasis on epidemiological and genetic studies of psychiatric and neurological disorders. We are now trying to extend such studies to a variety of other types of genetic disorder. Our recent work on osteogenesis imperfecta was designed to contribute to the understanding of the clinical, genetic, epidemiological, and sociomedical aspects of this disease in general and with particular reference to the Swedish population. From the public health viewpoint, it is essential to have a clear picture of how specific mutations affect different individuals in terms of disability and of how these mutations influence a variety of adaptive qualities. This aspect has often been insufficiently covered in genetic investigations. To give this aspect of the problem particular consideration in the present study, a specialist in social medicine and rehabilitation, Dr. R. Berfvenstam, was included in the team of investigators, which consisted of Dr. G. Smårs, an internist, and myself as research director. The work has been completed and has recently been published as a monograph.[1] In the following pages I shall summarize some of the main features.

Osteogenesis imperfecta—which has been known for quite some time as a dominant disorder—is a disease or syndrome with considerable variation in symptomatology as well as subsequent disability. This is a common phenomenon in clinical genetics which enforces provisional definitions of propositi and secondary cases. The following criteria were used:

For propositi: (1) blue sclerae and brittle bones as shown by one or more

1 Smårs, G., *Osteogenesis Imperfecta in Sweden*, Scand. Univ. Books, Svenska Bokforlaget, Stockholm, 1961, 239 pp.

fractures from inadequate trauma, or (2) brittle bones as shown by at least seven fractures from inadequate trauma.

For secondary cases: (1) relatives with the same criteria as the propositi, or (2) relatives with less severe manifestations, such as blue sclerae alone or multiple fractures from inadequate trauma.

The investigation covers the period from 1943 to 1957, with a census deadline of January 1957, and combines longitudinal and cross-sectional studies. The propositi were ascertained through special inquiry to the directors of the clinical divisions to which the patients in whom we were interested could be admitted and to all district physicians (70-percent reply). After the exclusion of those patients who were not eligible according to our criteria, the yield was 147 propositi, of whom 112 were living. Complete family records (parents and siblings) were obtained for all propositi through the parish record offices. The field investigation, which covered the whole country, led to the discovery of 127 secondary cases, of whom 78 were living, thus bringing the total of personally examined patients up to 190. Of this number, 136 also had hospital records. An additional 557 parents and siblings were investigated and found to be free of symptoms or signs of the disease.

All but seven of the secondary cases had symptoms too slight according to our criteria to have been reported. Thus the registration can be considered fairly complete. The ratio reported/expected propositi is .96.

The estimate of the prevalence of osteogenesis imperfecta in Sweden was approximately 300 cases in a population of 7.4 million (1 in 25,000). With the technique used, this means that just over 60 percent were recorded. The losses were probably due to delayed manifestation in the youngest age groups and to incomplete ascertainment in the older age groups, which, of course, were covered relatively less by the longitudinal survey. In many cases, the disease goes into an inactive phase during which the patient does not seek medical advice. Despite these deficiencies, the data may be considered reasonably representative. From the genetic viewpoint, this is indicated by the fact that we had no significant loss of families with one affected child.

The clinical analysis was based on the 190 surviving patients and on 22 lethal cases for which adequate information was available. It is worth noting that only 19 percent of the patients were severely handicapped as indicated by great difficulties in locomotion or by dependence on a wheel chair. The main clinical features were bone fragility (96 percent), blue sclerae (84 percent), impaired hearing (23 percent), and hyperlaxibility (45 percent). Most of the fractures occurred during the second and third years of life. Starting with the age groups of 15-20 years, the fracture frequency is greatly reduced. A careful and exact treatment of the fractures is very important for preventing unnecessary disability. The accumulated risk of deafness reaches a high of about 50 percent at the age of 60.

In 65 families, bone fragility always occurred with blue sclerae, and one parent

was consistently affected. The Mendelian ratio, calculated by various methods, came very close to 1 : 1, with no significant sex differences. These data included 13 chains of three generations which were examined personally. No skipping of generations was found. Bone fragility without blue sclerae occurred in only seven families, but still one parent was always affected.

In five families with two or more affected children, both parents were unaffected. The lack of consanguinity and the findings in one of these families are arguments against a special recessive type. Among the six children there were three girls and one boy affected and two boys unaffected. For one of the affected daughters the nominal father could not be the girl's biological father because of exclusions by both the MN and Rh systems. The probability that the unknown biological father should have been heterozygous for an identical hypothetical gene is remote. The mother disclosed the fact that at the age of 18 she had had a leg fracture with dubiously adequate trauma. Furthermore, she was found to have slight but definite left-sided deafness. Although these manifestations are insufficient for an accurate diagnosis, it seems likely that they were due to osteogenesis imperfecta.

Of the 266 cases of Swedish birth—*i.e.*, including the deceased ones—72 were sporadic; among these sporadics, 16 were lethal. Thus, no significant surplus of lethals was found among the sporadics. On the whole, however, these sporadic cases were more severely affected. This probably means nothing, since very mild sporadic cases would not have been found with the technique that was used. Nine of these patients had a total of 18 children, of whom nine were affected. There is nothing to contradict the assumption that the sporadic cases belong to the same genetic entity as the familial ones. Furthermore, the sporadics were randomly distributed among different birth ranks, and no maternal age associations were found. All the familial cases and the sporadic ones over two years of age showed no increased mortality.

The fertility of affected individuals as compared with the general population in Sweden was estimated at about 60 percent of the normal. The geographic distribution was examined by birthplace and residence. No significant geographic accumulations were found, nor did we find any difference between sporadic and familial cases in this respect. The mutation rate, calculated by the direct as well as the indirect method, was estimated at about 1 per 100,000 loci per generation with all the relevant reservations. A similar estimate from Japan in 1956 by Komai and co-workers was 1 per 25,000.

Among the factors that possibly influence the mutation rate, we have looked at maternal age, birth rank, season of conception, place of residence, climate, parental disease, and radiation exposure, and we have had no significant findings. Some of the sociomedical aspects have already been mentioned. It was furthermore shown that this small section of the population occupies a disproportionately large number

of hospital beds. Special education at home or in boarding schools for the handicapped was necessary for 21 percent of the patients between the ages of 8 and 39. On the whole, these patients showed a slightly greater attendance at schools beyond the general public school level than the average adolescent in Sweden.

A relatively large number of the severely handicapped patients were surprisingly well adapted. The general mental state of the patient, his psychological balance, his attitude toward his own situation, and, not least, his intellectual capacity seemed to be more important factors than the reduction of physical abilities. The income level of the working individuals tallied fairly well with that of the average population. Housing standards were good.

Because the investigation of juvenile amaurotic idiocy in Sweden has not yet been completed, I shall limit myself to a few comments. The genetic and epidemiological features of this disease were thoroughly investigated 30 years ago by Sjögren.[2] The average morbid risk is still about 1 per 40,000 live births. Since this is a rare simple recessive condition, it is not surprising to find accumulations in certain geographic isolates. Our recent contributions are based on the possibility of diagnosing approximately 95 percent of the heterozygotes.[3, 4] The rather cumbersome method involves the examination of 500 lymphocytes in blood smears for the presence of fairly typical vacuoles. These vacuolized lymphocytes average 1 percent in heterozygotes and 20 percent in homozygotes. In the homozygotes, this examination makes a diagnosis possible prior to the development of clinical symptoms.

The current material[5] includes all families with at least one affected child registered since Sjögren's study,[6] as well as his old material. A sample of about 200 conscripts from all over the country and another sample of about 1000 hospital patients from the Lund University clinics have been screened for possible heterozygotes. Patients with infectious diseases and other conditions in which vacuolization may occur have been excluded. In both samples the incidence of individuals with vacuolized lymphocytes is about 4 percent. Although this figure appears to be much too high, it seems pointless to attempt an explanation until further details have been studied.

Of more interest is the fact that we have been able to test all individuals in a small geographic isolate with a population of only 74. The disease has been

2 Sjögren, T., Die juvenile amaurotische Idiotie. Klinische und erblichkeitsmedizinische Untersuchungen, *Hereditas, 14,* 1931, 197-425.

3 Rayner, S., Juvenile amaurotic idiocy, *Acta genet., 3,* 1952, 1-5.

4 Rayner, S., and Böök, J. A., Genetics and blood morphology in amaurotic idiocy, *Lancet, i,* 1958, 1077-1078.

5 Rayner, S., Juvenile amaurotic idiocy in Sweden. With particular regard to the occurrence of vacuoles in the lymphocytes of homo- and heterozygotes, Institute for Medical Genetics, Uppsala, Sweden, 1962. (In press.)

6 *Loc. cit.*

endemic here for a good many years, and 38 percent of the people, excluding the affected, show vacuolized lymphocytes. Although further work is needed to determine the reliability of the test, this seems to confirm its value.

In 1960 and 1961, other epidemiological investigations of non-neuropsychiatric nature were started. These are limited to regions with populations of half a million to one million. In one such region, about 500 individuals with the Pelger anomaly, and in another about 600 with palmar keratosis, have been registered.

SUMMARY

Two rare inherited diseases—osteogenesis imperfecta and juvenile amaurotic idiocy—have been subjected to complete epidemiological and genetic studies in collaboration with clinical specialists (Gunnar Smårs, M.D., and S. Rayner, M.D.).

Osteogenesis imperfecta exemplifies a dominant defect with an incidence of about 1 per 25,000, with no regional or stratified preference. The mutation rate was estimated at about 1 per 100,000 loci per generation. The genetic and social aspects of the disease are discussed.

In 1931, juvenile amaurotic idiocy was thoroughly investigated by Sjögren. The recent investigation by Rayner was designed partly to compare the epidemiological picture of today with that of a generation ago. Because of the possibilities of diagnosing most of the heterozygotes by their vacuolized lymphocytes (detected by Rayner in 1952), some new features of the genetics and epidemiology could be analyzed.

STERN: We shall have a discussion at the end of all papers, so I call on Prof. Freire-Maia from Brazil.

N. FREIRE-MAIA

The Effect of the Load of Mutations on the Mortality Rate in Brazilian Populations

A series of investigations indicate that the mean number of lethal equivalents per person is roughly about four in several countries. Our data, however, obtained in Brazil in February and March of 1959,[1, 2] deviate widely from this value, with Whites showing an extremely low number (below 1) and Negroes showing a rather high one (about 9). The Whites were almost exclusively of Portuguese

1 Freire-Maia, N., Freire-Maia, A., and Quelce-Salgado, A., Lethal mutations in Brazilian human populations, *Nature, 189*, 1961, 80-81.

2 Freire-Maia, N., Deleterious mutations in man, *Eug. Quart., 7*, 1960, 193-203.

origin, and the Negroes supposedly derived from different regions of Africa. I intend to present here a summary of the findings I obtained a few months ago, in a different sample, from the same region previously investigated—*i.e.*, in the south of the state of Minas Gerais. (A full account of this work will be presented elsewhere.[3])

Minas Gerais is a predominantly rural region, with large coffee plantations and intense dairy activities. The seats of the *municipios* are small towns, with populations largely rural in their origins and/or main activities. Most of the residents are Roman Catholics, and a small proportion are Protestants and Spiritualists. Birth control practices are generally nonexistent in the lower social strata, which include urban and rural unskilled workers. These workers contributed with the largest fraction to the sample previously studied as well as to the one recently obtained.

In the present investigation, the technique of our previous survey[4, 5] has been modified slightly:

1. The area now being investigated is larger, including six instead of three *municipios*.

2. The present sample is predominantly urban by residence rather than largely rural, as in the previous survey, and only a few farms have been visited.

3. In 1959, efforts were made to include only the lowest social levels, where Whites and Negroes appeared to exist in rather similar socioeconomic conditions. As a matter of fact, mortality rates in the five control subsamples analyzed in our previous paper showed insignificant differences. In the present investigation, although the lower social classes were generally included, no effort was made to minimize the social gap between Negroes and Whites. It is therefore expected that, in our present sample, Whites should occupy a somewhat better mean social position than Negroes.

4. The questionnaire has remained almost unchanged except for the question on consanguinity between the spouses. This question is now posed at the end of the interview instead of at the beginning.

5. In 1959, all the data were collected personally by the authors. In the present survey, the author was responsible for only 5 percent of the interviews. The remaining field work was carried out under the author's supervision, by women who were duly instructed.

As expected, inbreeding rates in our present predominantly urban population are appreciably lower than in the previous rural one. Because of the small size of some consanguineous subsamples, the data have been pooled to form only three classes: White × White, White × Non-White, and Non-White × Non-White. Whites are almost entirely of Portuguese ancestry (there is an extremely low proportion of families from other stocks) and Non-Whites include Mulattoes and

3 Freire-Maia, N., The load of lethal mutations in White and Negro Brazilian populations. II. Second survey, 1961. (In preparation.)

4 Freire-Maia, N., Freire-Maia, A., and Quelce-Salgado, A., *loc. cit.*

5 Freire-Maia, N., Deleterious mutations in man, *loc. cit.*

Negroes. This picture is completely different from the one prevailing in south Brazil, where Italians, Germans, Arabs, Poles, Japanese, and other groups contribute appreciably to the population.

The groups mentioned above (W × W, W × NW, NW × NW) have been classified according to the general aspect of the spouses. This may not represent the real situation under investigation, not only because of misclassification of borderline cases, but also because inbreeding studies reflect the genotype of the common ancestors, who have not been classified. The W × NW consanguineous couples include 28 Whites, 25 light Mulattoes, 1 dark Mulatto, and 2 Negroes. Thus, this sample contains a much larger proportion of Caucasian genes than African genes. On the other hand, the NW × NW consanguineous group is a more African sample, for it contains 39 Negroes, 15 dark Mulattoes, and 26 light Mulattoes.

The present study includes 1926 families, with a total of 12,086 pregnancy terminations. On the average, consanguineous couples marry 1 to 2 years younger than nonconsanguineous couples. The mean duration of marriage to the day of the survey is consistently 4 to 5 years longer in the consanguineous group than in the control group. In the three ethnic subgroups, however, the mean marriage age and the mean time elapsed since marriage are approximately the same.

Illiteracy is very high in the population investigated, and it increases from W × W to NW × NW. The heterogeneity in this respect is highly significant. A comparison of the frequencies of illiterate parents in the control and consanguineous subsamples revealed only two significant differences: higher frequency in the W × W nonconsanguineous group and in the NW × NW consanguineous one. A similar phenomenon was observed in our mostly rural first survey, where the Negro × Negro fraction, extracted from NW × NW, showed a different distribution from the total NW × NW groups. (This heterogeneity was not significant.) This shows that the high inbreeding effect on mortality, detected among Negroes, may not be ascribed to socioeconomic variables that could, perhaps, be measured by illiteracy rates. Furthermore, some unpublished information obtained on the Negro fraction of our first survey did not suggest that the consanguineous couples live under more adverse socioeconomic conditions.

Fecundity (here defined as the mean number of pregnancy terminations per couple with at least one pregnancy termination) is about the same in the three groups, W × W, W × NW, and NW × NW, but it is significantly higher among the consanguineous couples than among the nonconsanguineous ones. This is probably due to the fact that the time elapsed since marriage is also higher for the consanguineous couples. The mean fecundity for year of union (about 0.33) is about the same in all the categories.

Mortality has been subdivided into three categories—namely, abortions plus miscarriages, stillbirths, and mortality from birth up to and including the age of 20 in both sexes. The rates of postnatal mortality referred to here may be accepted

as virtually comparable to those previously obtained[6] for mortality before the mean marriage age. Calculations have been made exactly as in our previous papers[7, 8]—*i.e.*, the frequencies of abortions plus miscarriages, on the basis of pregnancies (twin pregnancies being taken as one); the frequencies of stillbirths, on the basis of children born (twin births being taken as two); and mortality after birth, on the basis of liveborn children.

The differences in the mortality rates detected in the three control subsamples are statistically not significant for abortions plus miscarriages, where the White group shows a somewhat higher frequency; but they are significant for stillbirths, for postnatal mortality, and for the total, with Non-Whites showing the highest mortality rates. This is a consequence of the fact that, in our present sample, as has already been pointed out, Whites were expected to occupy a somewhat better mean socioeconomic position than Non-Whites. In the control group of NW × NW, total mortality is about 0.31. This value is very close to the 0.29 observed in the control group of W × W. In seven out of the twelve comparisons made (including the totals), mortality in the inbred subsamples is higher than in the controls. But it is only among Non-Whites that this difference is significant at the levels of 0.01 and 0.0001. (For abortions plus miscarriages, postnatal mortality, and the total, see Fig. 45.)

Genetic loads, in terms of lethal equivalents, have been estimated according to the method of Morton, Crow, and Muller.[9] The figure obtained for W × W confirms the previous working hypothesis that the mean number of lethal equivalents per White individual is lower than 1. (Our present estimate is 0.81 ± 0.86.) The low value detected among W × NW couples (0.18 ± 2.16) appears to reflect the rather small genetic load of Whites. For NW × NW families, the estimate obtained (8.97 ± 2.20) attests to the relatively high number of lethal equivalents prevailing among Negroes. On the basis of the present data, this number has been estimated to be about 12.[10] This estimate is in agreement with that of 10.21 ± 4.93, the total for Negroes calculated from the data of the first survey. The load of lethal equivalents found among Negroes is significantly different from that estimated for Whites. It is impossible to envisage, with a reasonable degree of accuracy, the factors that operated in producing the picture disclosed by our data. This problem will be discussed elsewhere.[11, 12]

These data refer exclusively to the populations living in the area studied and

6 Freire-Maia, N., Freire-Maia, A., and Quelce-Salgado, A., *loc. cit.*

7 *Ibid.*

8 Freire-Maia, N., Deleterious mutations in man, *loc. cit.*

9 Morton, N. E., Crow, J. F., and Muller, H. J., An estimate of the mutational damage in man from data on consanguineous marriages, *Proc. Nat. Acad. Sc., U.S., 42,* 1956, 855-863.

10 Krieger, H., and Freire-Maia, N., Estimate of the load of mutations in homogeneous populations from data on mixed samples, *Genetics, 46,* 1961, 1565-1566.

11 Freire-Maia, N., The load of lethal mutations in White and Negro Brazilian populations. II. Second survey, 1961. (In preparation.)

12 Krieger, H., and Freire-Maia, N., The effect of the mutational load on the mortality rate in man, *Acta genet., 12,* 1962, 97-102.

cannot be extrapolated uncritically to other regions and ethnic groups. As a matter of fact, the genetic load of Whites in south Brazil (who have a different and highly heterogeneous origin) lies between those of Negroes and Whites in Minas Gerais.[13] The phenomenon observed in Minas Gerais may be purely local and reversible.

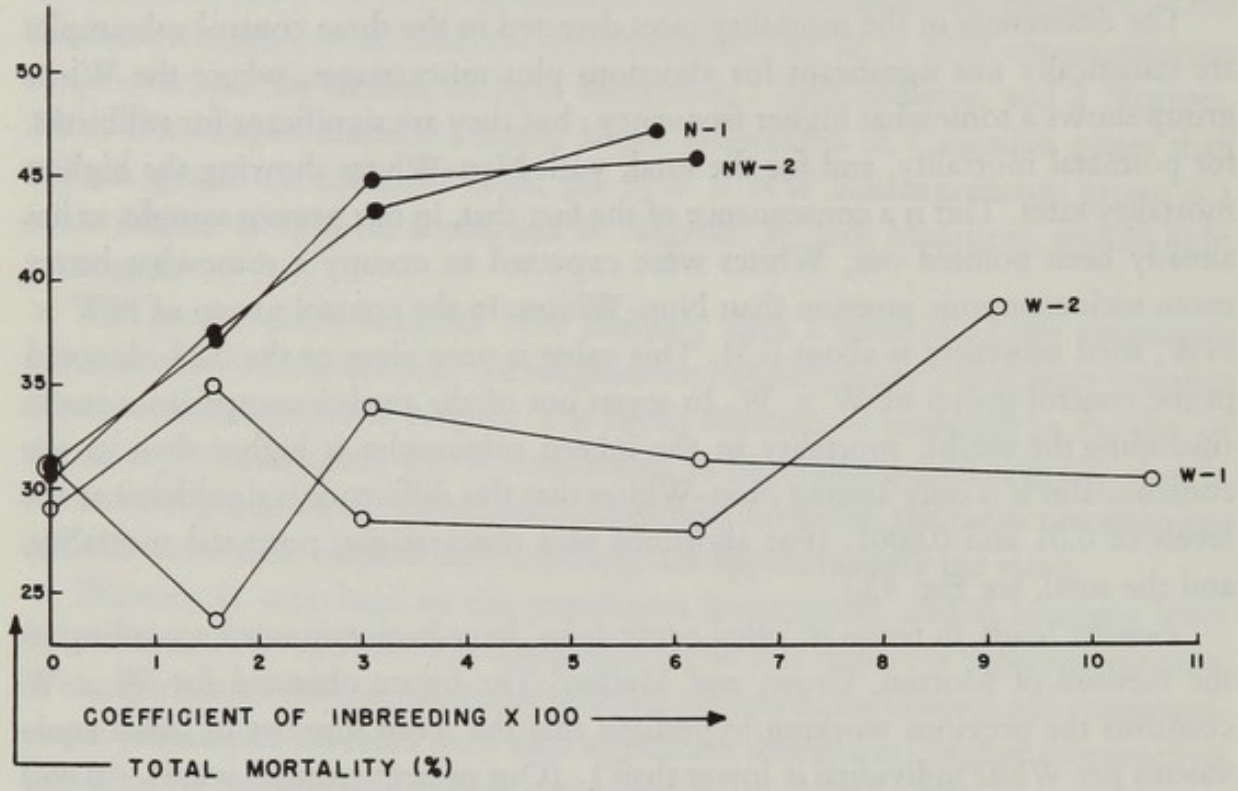


FIG. 45. Total mortality (from abortions to postnatal mortality, as defined in the text) plotted against 100F. Number 1: data from the first survey (see footnotes 1 and 2). Number 2: data from the second survey. W: Whites, N: Negroes.

I should like to make a few comments on an important parameter—namely, the ratio of B to the genetic component of A, as suggested by Crow.[14] Since a method for the calculation of the genetic component of A is not yet available, an approximate total value of A is being used. We know, however, that the ratio of B to the genetic component of A is higher than the ratio of B to total A. In our present data, this ratio is about 1 for Whites and about 12 for Non-Whites. Therefore, the ratios we are looking for must be higher than 1 in Whites and higher than 12 in Non-Whites. We do not know how much higher they are, but it is known that they must be lower than B/A_m, as defined in other papers.[15,16] The present data suggest that the mutational load—*i.e.*, the load contributed by

13 Marcallo, F. A., Simões, I. A., Freire-Maia, N., and Azevedo, J. B. C., Inbreeding effect in an urban south Brazilian population, Second International Conference on Human Genetics, International Congress Series No. 32, Excerpta Medica Foundation, 1961, E78.

14 Crow, J. F., Some possibilities for measuring selection intensities in man, *Human Biol., 30,* 1958, 1-13.

15 Krieger, H., and Freire-Maia, N., Estimate of the load of mutations in homogeneous populations from data on mixed samples, *loc. cit.*

16 Freire-Maia, N., Mutational load in man, *Acta genet.,* 1962. (In press.)

genes which are detrimental in homozygotes and not beneficial in heterozygotes—may be more important than the segregational load—*i.e.*, the load formed by overdominant genes—in the composition of the lethal equivalents found in the Brazilian populations studied.

These considerations have obvious and serious implications with regard to the genetic damage from ionizing radiations. Inbreeding depression is now widely used to estimate the existing genetic load. Any increase of this load by a rise in the radiation level will be more deleterious if the load is mainly mutational instead of segregational.

STERN: Thank you. These first two papers dealt with empirical analyses of human populations, but Dr. Freire-Maia's interpretation of the data also involved general questions relating to genetic load. The next two papers, by Dr. Morton and Dr. Slatis, will deal particularly with aspects of the fundamental assumptions underlying the problem of the genetic load.

N. E. MORTON

The Components of Genetic Variability

The assumed distribution of genes contributing to the inherited loads of populations may be shown in a simple diagram (see Fig. 46). The relative magnitudes of the two classes of genes, as indicated in Figure 46, are quite arbitrarily chosen. It is likely that the number of loci at which alleles are maintained by mutation is greater—I think perhaps much greater—than the number at which polymorphic systems are maintained by heterozygote advantage, although the figure does not show this. Also, the degree of overlap is uncertain. There may be genes maintained by mutation pressure which have rather high frequencies and tail out into the common polymorphisms. And, similarly, it is possible that there are a number of genes maintained by heterozygote advantage at quite low frequencies.

The problem is even more complex, because we can readily imagine a third distribution—between the two curves of Figure 46—presenting genes of a mixed type, which require both mutation and heterozygote advantage to be maintained at their present frequencies. Moreover, there may be genes whose frequencies are changing rapidly from rare to common or vice versa. We may, of course, throw up our hands and simply declare that it is not possible or profitable at present to try to sort genes into two types. It is even doubtful whether the classification is logically valid. But so pessimistic a point of view is contrary to the usual philosophy in science. When faced with complexity, the investigator attempts to keep

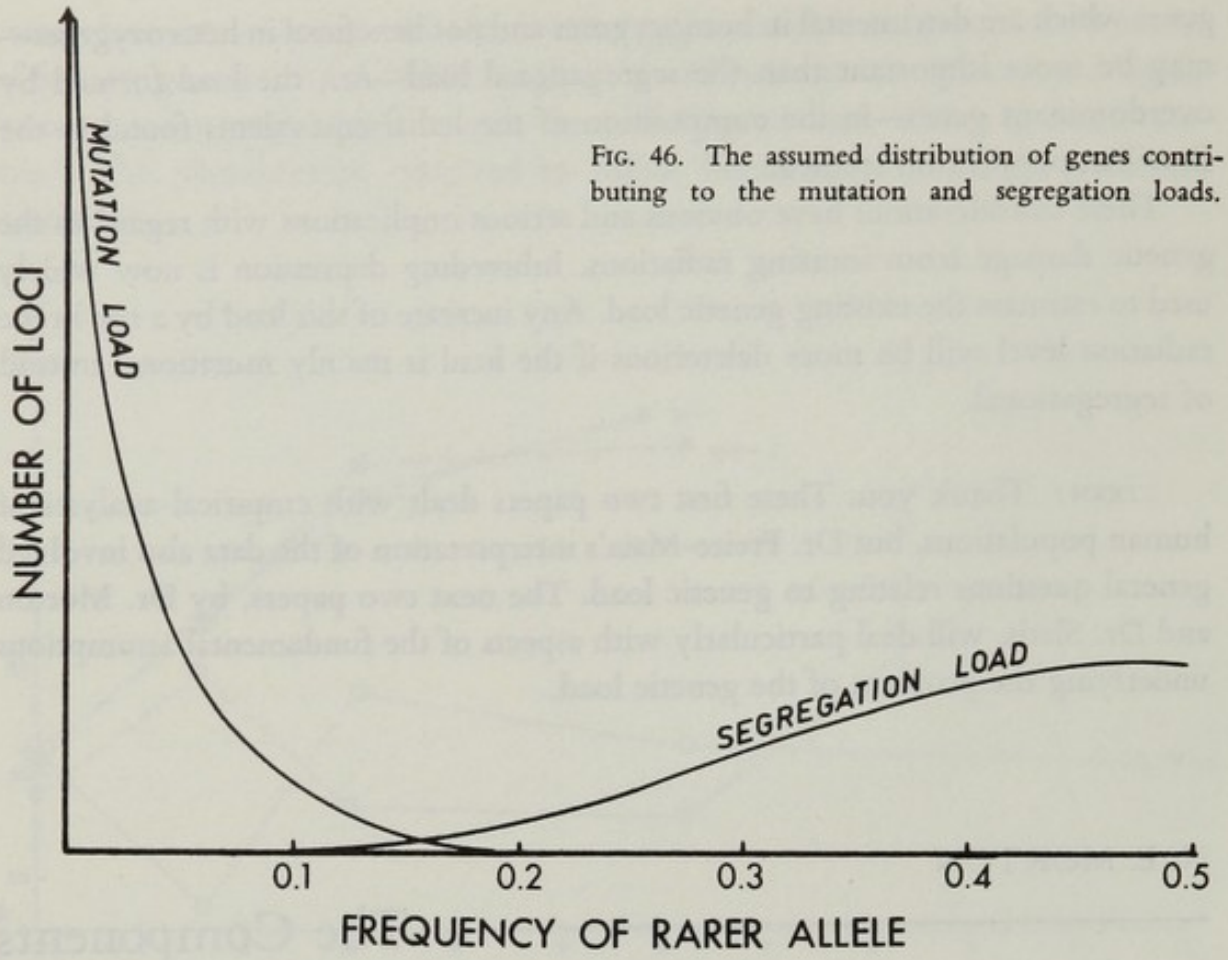


FIG. 46. The assumed distribution of genes contributing to the mutation and segregation loads.

his hypothesis extremely simple. Let me discuss some of the hypotheses that have been proposed regarding the components of genetic variability and come to some understanding of what part of it is maintained by mutation and what part by heterozygous advantage.

The first attempt to deal with this problem may have been Ford's definition of polymorphism.[1] I venture to give a rather free version of the original dictum: Polymorphism is a genetic discontinuity maintained by selection in frequencies such that the rarest of the alleles could not be held in the population by recurrent mutation. This means that we can assign all rare genes essentially to mutation and all common genes to heterozygote advantage. This attitude may haen been due to the state of population genetics in those years. There was a contest between two schools, one emphasizing the importance of drift and the other stressing the power of selection. So Ford's definition was a fiat; he said that polymorphisms are adaptive. He did not mention the exceptional rarer genes that may be maintained by selection, and he disregarded, for the moment, the polymorphisms that may be maintained, transiently, by mutation or drift. Some sort of balance is now being achieved, since it is recognized that selection is indeed the most interesting mechanism to study, although drift will often confuse the picture and can easily be demonstrated.

1 Ford, E. B., Polymorphism and taxonomy, in J. S. Huxley (ed.), *The New Systematics*, Clarendon Press, Oxford, 1940, pp. 493-513.

Ford's tendency to recognize a polymorphism only where both alleles are common has been questioned from two points of view. Rare genes may represent heterozygote advantage; common genes may represent mutational balance. And, furthermore, where the cutting point between common and rare genes should be is by no means clear. What frequency is so large that it could not be maintained by recurrent mutation? It was pointed out, more than thirty years ago, that a purely mutational balance is possible between opposite mutation rates. If gene A mutates to A′ with rate U and the reverse rate is V and nothing else is acting on the system, then equilibrium will be established when the ratio of the gene frequencies is the ratio of mutation rates. It is thus clearly not possible to take some arbitrary frequency, such as an incidence of one in a thousand, and agree that any lower frequency is due to mutation and any higher frequency to heterozygote advantage.

A final decision, of course, must be based on the demonstration of the directions and exact magnitudes of the forces operating in any particular system. This knowledge is attained but slowly, and some other approach seems useful at the present time. Although a radical simplification can be made, it may well be wrong. The important thing is that it be simple enough to be tested. The simplification that has been proposed is that the genes that cause a measurable inbreeding decline are predominantly the rare genes of the mutational load. This claim is in essential agreement with Ford's idea that the rare genes in general are the ones contributing to the mutational load, but it suggests consanguinity analysis as a method for separating the mutational component from the over-all load. I do not think we can say that this hypothesis is correct, but we can say that it is the most useful hypothesis to test at the present time. If it is wrong, it may be disproved and rejected; if it is right, it is a simple hypothesis which leads to many interesting results.

Now, this is, in essence, the theory of lethal equivalents: Consanguinity is a tool to isolate the mutational load. The rest of the theory consists of mere trappings involved in getting estimates of the load and interpreting them.

Several models have been suggested for the effects of consanguineous marriage. Table I illustrates the classical mutational-load model. The homozygote G′G′ is assumed to be the best of the three genotypes, and the other types suffer some disadvantage by comparison with this homozygous type with respect to either mortality or fertility. (There has been some confusion about the word "load." Some people, such as Owen, felt it ought to have some social significance. I maintain that it is a genetic rather than a sociological concept, since, at this point, we are simply evaluating certain genetic properties.) F is the inbreeding coefficient, q is the gene frequency, and s is the disadvantage of GG relative to G′G′. In other words, if the reproductive potential of the optimum genotype is unity, the potential of the others is $1 - s$. The degree of dominance of G in the heterozygote is denoted by h. In the mutational-load model, h is taken to be zero or positive, so that the heterozygote is either equal to or inferior to the favored homozygote. The

load can be represented as a linear function of the inbreeding coefficient provided the genes act independently to a first approximation. This hypothesis is not so limiting as it appears, because interactions of rare recessive genes with common genes involve higher order terms of F, which should be negligible at low levels of inbreeding. So we need be concerned only with the interaction of rare genes with one another. If both genes are sufficiently rare—and each one has its own independent effect—then the interaction can be neglected. The total genetic load is simply the sum of the frequencies of the deleterious gene weighted by their homozygous disadvantage. When there is no inbreeding in the population, the

TABLE I

THE MUTATIONAL LOAD

Genotype	GG	GG′	G′G′
Frequency	$q^2(1-F)+qF$	$2q(1-q)(1-F)$	$(1-q)^2(1-F)+(1-q)F$
Fitness	$1-s$	$1-hs$	1

Expressed genetic load $= A + BF$ lethal equivalents per zygote.

Total genetic load $= \Sigma qs$ lethal equivalents per gamete.

$$A = \Sigma q^2 s + 2q(1-q)sh$$

$$B = \Sigma qs - \Sigma q^2 s - 2q(1-q)sh$$

$$B < \text{total genetic load} < A + B$$

load is represented by A. This is made up of an environmental component, a component due to selection against homozygotes, and a component due to selection against heterozygotes. It also includes maternal-fetal incompatibility, as well as segregational and substitutional loads. B is the contribution of inbreeding to the load; it is the total load minus the genetic part of the random load. So the total load lies between B (which in a valid study is certainly genetic) and A plus B, which includes the environmental components.

Table II shows the principal alternative to the mutation model, in which the heterozygote rather than one of the homozygous types is optimal and both homozygotes suffer some impairment as compared with the heterozygote. It turns out that again the load is a linear function of the inbreeding coefficient, if we can neglect interactions with other loci, and these relations come out again in a simple way. The estimate of the total genetic load obviously depends upon the environment with which the genes interact and also upon the history of the population, but it does not require that the population be at equilibrium.

This is how the loads A and B are evaluated. Let us suppose that the chance of surviving the load imposed by the first locus we consider is $1 - L_1$ and the chance of surviving the load imposed by the second locus is $1 - L_2$. If they act independently, the whole chance of survival is going to be the product $\prod_i (1 - L_i)$ for as many loci as contribute loads. And if these loads are small and the number of loci is large, then it is a well-known fact that this is going to be a good approximation to $e^{-\Sigma L_i}$. In this sense, loads are said to be additive, by virtue of the assumption

that, to a first-order approximation, interaction between these loci can be neglected. And it can be shown that on this assumption, for both mutational and segregational loads, the load has a linear regression on the inbreeding coefficient.

The interest of this model depends to a considerable extent on the assumption that we can interpret the effects of inbreeding in mutational terms. Table III was compiled from a variety of sources and from differing environments. It does not include some of the most recent data reported at this meeting. As Dr. Goldschmidt mentioned (see p. 191), and as has been emphasized for many years, the load depends upon both the history of the population and the present environment; if

TABLE II

THE SEGREGATIONAL LOAD

Genotype	G^iG^i	G^iG^j	G^jG^j
Frequency	$q_i^2(1-F)+q_iF$	$2q_iq_j(1-F)$	$q_j^2(1-F)+q_jF$
Fitness	$1-s_i$	1	$1-s_j$

Expressed genetic load $= A + BF$ lethal equivalents per zygote.

Total genetic load $= qs$ lethal equivalents per gamete.

$A = \Sigma q^2 s$

$B = \Sigma qs - \Sigma q^2 s$

$B <$ total genetic load $< A + B$

the environment changes, presumably the load will change. The largest estimate is based on very old data, which may not be very good, and which pertain to a population with many more deaths from infection than were reported in any of the later studies. This estimate may thus lie at the upper limit of measurable loads. In Table III, under *B*, we find a series of estimates of genetic loads. The average zygote has a little over one gene which when made homozygous would cause mental deficiency. If we consider only the genes that cause severe mental deficiency, the estimate comes to about one-third of this, or one-fourth per gamete and one-half per zygote. Estimates such as these allow the statement that the average zygote carries at least several recessive genes which, if made homozygous, would cause severe impairment or death. These are carried in single dose for the most part, and the medical effects in heterozygotes have not begun to be understood.

It should be noted that the ratio B/A tends to be rather large, and this is the basis of an argument that the load is mutational. For a segregational load maintained by heterozygote advantage, if we are measuring fitness—and that is a critical assumption—it can be shown that, at equilibrium, B/A will be equal to the number of multiple alleles maintained at each locus by heterozygote advantage. If we were measuring fitness here, rather than one of its components, then we would have to be willing to assume a great many alleles maintained by heterosis at each locus—so many, in fact, that it is unlikely that isolates of the size that have been discussed during this meeting would be able to maintain so many genes. It is

TABLE III
ESTIMATES OF A AND B

	A	B	B/A
Schull:[2] major congenital malformation	.0102	0.093	9.1
Sutter:[3] abnormality	.0443	2.196	49.6
Slatis *et al.*:[4] abnormality	.1033	1.164	11.3
Böök:[5]			
genetic abnormality	.0821	2.020	24.6
mental deficiency	.0129	0.694	54.0
Bemiss (1858):[6] abnormality	.1067	5.792	54.3

important to realize that we are measuring only certain components of fitness, and any part of fitness which acts outside the range considered, which is not expressed as juvenile abnormality or mental deficiency or one of these other elements, could contribute to both A and B and change the final ratio considerably. However, to accommodate these high B/A ratios with a segregation load hypothesis, we must be prepared to assume that one of the two homozygous classes is not impaired during the phase being investigated (from birth through adolescence) but may be affected at other stages of the life cycle, perhaps by reduced fertility or diminished chance of early fetal survival, and that the loss suffered through these components is severe.

There are other methods of estimating A and B. The earlier data were compiled by investigators who collected children, by one means or another, from consanguineous marriages and then determined a rather common defect in these different classes of consanguineous marriages. These were *prospective* studies, in which consanguinity was determined first and abnormality second. In a *retrospective* study, the sequence is reversed. You determine the abnormality first and then ask about consanguinity. This method has its own hazards, but it can, if applied correctly, yield estimates of A and B. You can estimate the incidence of the trait or class of traits that will be of this type. Let α be the mean inbreeding coefficient and let σ^2 be the variance of the inbreeding in the general population. I, the incidence of the disease, may be expressed as follows:

$$I = A + B\alpha$$

F, the average inbreeding coefficient of affected zygotes, will be

$$F = [A\alpha + (\sigma^2 + \alpha^2)B] / I$$

These two equations can then be solved for A and B:

2 Schull, W. J., Empirical risks in consanguineous marriages: sex ratio, malformation, and viability, *Am. J. Human Gen., 10,* 1958, 294-343.
3 Sutter, J., *Recherches sur les effets de la consanguinité chez l'homme,* Declume Press: Lons-le-Saunier, 1958.
4 Slatis, H. M., Reis, R. H., and Hoene, R. E., Consanguineous marriages in the Chicago region, *Am. J. Human Gen., 10,* 1958, 446-464.
5 Böök, J. A., Genetical investigations in a North Swedish population. The offspring of first-cousin marriages, *Ann. Human Gen., 21,* 1957, 191-221.
6 Bemiss, S. M., Report on influence of marriages of consanguinity upon offspring, *Trans. A.M.A., 22,* 1858, 319-425.

$$A = I - Ba$$
$$B = I(F - a) / \sigma^2$$

It has been shown that this method can be improved to arrive at a maximum-likelihood solution if one aims at greater accuracy.

Table IV exemplifies the application of this retrospective method to three defects: limb-girdle muscular dystrophy, congenital deaf-mutism, and low-grade mental deficiency. We have some additional data on low-grade mental deficiency in Wisconsin which are reasonably consistent with these. The procedure in determining these numbers is quite simple. The incidence and the average inbreeding coefficient of probands can be determined. We can find out what proportion of cases are nonrecessive (*i.e.*, sporadic) by two principal methods. The first is to compare the inbreeding coefficients of isolated and familial cases. If there are sporadic cases not associated with inbreeding, then isolated cases will have a lower inbreeding coefficient than familial ones, and the proportion of sporadic cases can be determined by the difference in inbreeding coefficient. A more precise estimate, which fortunately agrees with the first, can be obtained by segregation analysis, in which you set out to determine simultaneously the segregation frequency, the proportion of sporadic cases, and any other parameters of genetic interest. From these numbers, the total gene frequency and the total frequency of the trait in a randomly mating population can be calculated easily.

The segregation analysis in all three conditions shows that when the sporadic cases are removed there is a close approximation to a 3:1 ratio. These genes, therefore, are acting with high penetrance, so that we can deal directly in terms of gene frequencies instead of loads, where the gene frequencies are weighted by penetrance or selection. By adding all these frequencies, it can be shown that about one gamete in four carries a gene which, if made homozygous, would cause one of these defects. This is, presumably, a very small fraction of the recessive load, and it accounts for very little morbidity.

Now, other arguments can be brought to bear that would support the hypothesis that evaluation of consanguineous marriage is a knife that will cut out the

TABLE IV

ESTIMATES OF Σq AND Σq^2

	All estimates multiplied by 10^5				
	All cases		*Nonrecessive*	Σq	Σq^2
	I	$\overline{F}$	*cases (I)*		
Morton and Chung:[7] Limb-girdle muscular dystrophy	7	469	3	800	3
Stevenson and Cheeseman, after Chung, Robison, and Morton:[8] Congenital deaf-mutism	31	534	10	8,000	18
Dewey and Morton:[9] Low-grade mental defect	361	169	304	18,500	48

[7] Morton, N. W., and Chung, C. S., Formal genetics of muscular dystrophy, *Am. J. Human Gen., II,* 1959, 360-379.

[8] Chung, C. S., Robison, O. W., and Morton, N. E., A note on deaf mutism, *Ann. Human Gen., 23,* 1959, 357-366.

[9] Dewey, W. J., and Morton, N. E., Recessive genes in low-grade mental defect. (In preparation.)

mutational load and will allow examination of it. One is that you get very good agreement in mutation rates for recessive genes and dominant and sex-linked genes, as estimated by completely different methods.

These mutation rates are presented in Table V. The selection coefficients (s) are based on the number of children left by affected people. The mean gene frequency and the number of loci can be estimated very easily from the total gene frequency and the total squared gene frequencies, if we assume that there is not a

TABLE V

ESTIMATES OF MUTATION RATES, GENE FREQUENCIES, AND NUMBERS OF LOCI

	Selection coefficient s	*Mean gene frequency* Q	*Number of loci* n	*Mutation rate per gamete* $U \times 10^5$	*Mutation rate per locus* $u \times 10^5$
Limb-girdle muscular dystrophy	.75	.0044	2	6	3.4
Deaf-mutism	.68	.0023	35	45	1.3
Low-grade mental defect	.97	.0026	71	155	2.2

great deal of variation in gene frequencies. The opposite assumption has certain predictable effects: If the gene frequencies vary widely, this would tend to underestimate the number of loci and overestimate the mean gene frequency. The estimates in Table V were calculated assuming that the genes were effectively recessive but allowing for the fact that the inbreeding coefficient in the past was higher than it is at the present time, assuming, in fact, an inbreeding coefficient of 0.006 as found by Neel in some isolated populations. It is higher in some populations and less in others and we know very little about the inbreeding coefficient in long-established populations.

I shall make no attempt to defend these assumptions, but the important thing for the moment is that they lead to estimates of mutation rates which are quite consistent internally and also show reasonable agreement with mutation rates of dominant and sex-linked recessive genes, in Drosophila, man, and the mouse. If these rates are wrong, then either we have a whole tissue of coincidental errors or else the dominant and sex-linked mutation rates estimated so carefully by Dr. Neel and others are wrong too, since they agree so closely with the present estimates.

In any event, the assumptions required to estimate a recessive mutation rate are different from, but not demonstrably less plausible than, those required to estimate a dominant or sex-linked mutation rate. For the dominant case some generally unprovable assumptions have to be made about the proportion of sporadic cases that are mutants rather than phenocopies and about illegitimacies, cases of incomplete penetrance, and so on. I think, therefore, that the agreement between these different methods lends some support to the idea that the theory is not too far off.

Another argument in support of the contention that genetic loads are mainly mutational is based on the theorem that traces back to Wright and Crow and

myself and has been stated in its most general form thus far by Crow,[10] in which a purely selective system of any sort, not necessarily involving heterozygote advantage, imposes a certain load in a randomly mating population, a lower limit to which can be established in the following way: Take any allele and determine the disadvantage that it suffers in the homozygote and obtain the product of the gene frequency and the selective disadvantage, which then is a lower limit to the load due to that locus in a randomly mating population. From this theorem, you can demonstrate that a rather considerable load is exerted even by this small fraction of recessive genes, if they are maintained by the heterozygote advantage. If we admit that the number of serious, deleterious, recessive genes is not hundreds but probably thousands, then the load becomes inconceivably large on the assumption that the genes are acting independently. If in fact there is a high degree of synergism—that is, if a recessive gene gets eliminated only when in conjunction with many other recessive genes—this would reduce the actual load in the population. However, since the genes involved are extremely rare, it may safely be assumed that such interactions would have to be rather enormous to outweigh the much more common effects of the genes when they are not multiply homozygous.

It appears, therefore, that the available data are entirely consistent with the very simple assumption that inbreeding isolates the mutational load. I could advance some evidence from other organisms. In Drosophila it turns out that most of the load estimated in this way is due to genes that are fully lethal and very little is due to subvital genes. These genes are therefore drastic and rare, as you would expect mutational loads to be. In Drosophila we also have studies based on random lethals taken from natural populations which on the average are disadvantageous in heterozygotes as the mutational load leads us to expect.[11, 12]

An exception which in a way proves the rule is provided by what occurs in the honey bee[13] and some other Hymenoptera,[14] where there is an autosomal locus maintaining a balanced lethal system in controlling sex. Homozygotes are lethal males, heterozygotes are viable females, and hemizygotes are viable males. In this system, considering only the females, you get a B/A ratio of about 12, which agrees excellently with the estimate of the number of alleles known at this locus. This is an extreme case. It is a balanced lethal system, and therefore it ought to maintain the greatest possible number of multiple alleles. If this maximum number is only 12, then high ratios of B/A for systems which involve very little selection in comparison with a balanced lethal system are unlikely to be due to heterozygote advantage.

10 Crow, J. F., Some possibilities for measuring selection intensities in man, *Human Biol., 30,* 1958, 1-13.
11 Stern, C., Carson, G., Kinst, M., Novitski, E., and Uphoff, D., The viability of heterozygotes for lethals, *Genetics, 37,* 1952, 413-449.
12 Greenberg, R., and Crow, J. F., A comparison of the effect of lethal and detrimental chromosomes from Drosophila populations, *Genetics, 45,* 1960, 1153-1168.
13 Mackensen, O., Viability and sex determination in the honey bee, *Genetics, 36,* 1951, 500-509.
14 Whiting, P. W., The evolution of male haploidy, *Quart. Rev. Biol., 20,* 1945, 231-60.

It therefore appears that all data considered are consistent with this very simple mutation hypothesis. This demonstrates, at all events, that it is a useful hypothesis to pursue further and either prove or disprove. From Drosophila we have recently obtained evidence that detrimental genotypes produced by making a chromosome homozygous are due not to detrimental genes as such but to multiple homozygosity. This increases in frequency very rapidly with inbreeding in a nonlinear way. The smaller the inbreeding range that is studied, the less those detrimental genes contribute, so that virtually everything that is estimated at low values of inbreeding is a full lethal in Drosophila. But whether that means that the minor genes are ordinarily eliminated in multiple or single homozygotes or in heterozygotes, I do not know.

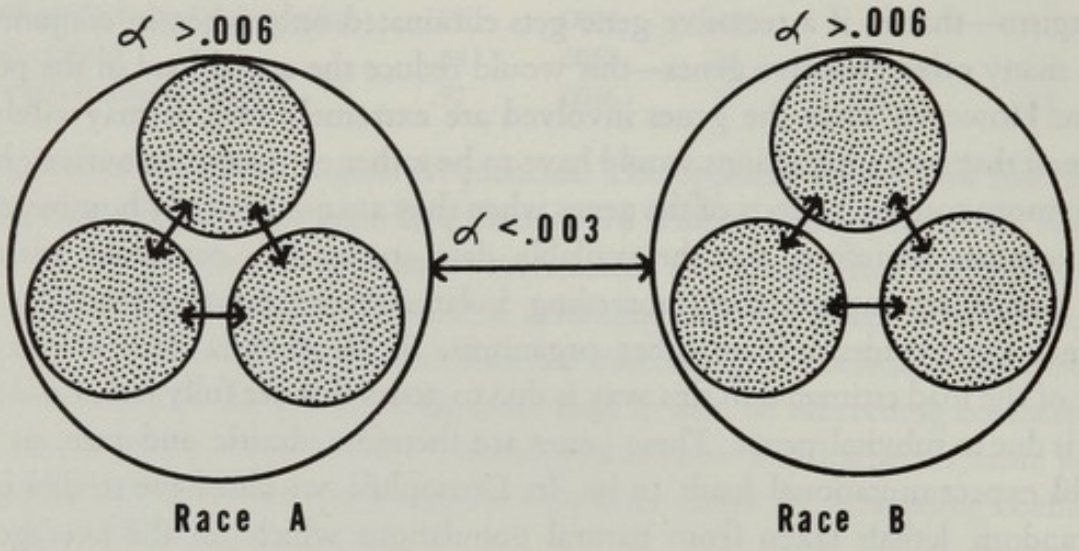


FIG. 47. Population structure in man.

Figure 47 takes us to an entirely different problem. We have been considering the effects of consanguineous marriage. The other side of the coin is outbreeding. Studies on isolates show inbreeding coefficients in small populations in the neighborhood of .006. This is certainly an underestimate, because it does not include the effect of remote consanguinity which is impossible to demonstrate by written records. It would presumably require a biological indicator to arrive at an estimate of that. But we can say that the amount of inbreeding among local populations in a fairly sedentary population is at least this much. In Hawaii we had the opportunity to study 180,000 births in a population in which one-third of the matings were outcrosses between races. We studied a number of conditions—congenital malformations and different types of mortality, birth weight, maternal weight and height, and so on—and it turns out that there is no consistent effect of outcrossing in this population. It seems, on the basis of these data, that the total effect measured relative to inbreeding effects is less than that due to an inbreeding coefficient of .003 and may well be zero. This is the upper 95-percent confidence limit. Measuring in this way outbreeding effects as a fraction of inbreeding effects, we

can say that the genetic divergence between the major racial groups in Hawaii has a negligible effect on viability.

Now, it seems of some importance that no outcrossing effects are demonstrable in this material, because it has been proposed by Dr. Neel[15] that differences among races in specific malformation frequencies—such as the high incidence of spina bifida in Caucasians and the high incidence of cleft palate in Japanese—are due to multiple homozygosity in these populations. If this were true, one would expect a reduction of the malformation rate on outcrossing. This is not observed.

Furthermore, Table VI directs attention to a malformation which showed the greatest racial difference in international comparisons. This is spina bifida, which in Japanese has a rate that is only about one-sixth as great as in Caucasians. Now, this is not the time to discuss the validity of international comparisons of something which is not very clearly defined, but the interesting thing is that in Hawaii the

TABLE VI

SPINA BIFIDA IN CAUCASIAN AND JAPANESE INCROSSES

	Frequency per 100,000 Births	
Japanese (Neel)	21	
		$\chi^2 = 8.5$
Japanese (Hawaii)	49	
		$\chi^2 = 3.6$
Caucasians (Hawaii)	82	
		$\chi^2 = 5.7$
Caucasians (Neel)	129	

Japanese go up and the Caucasians go down; the convergence is not complete but very remarkable.

Considering that most of these Caucasians derive from the mainland United States as first-generation immigrants, I think the convergence is so great that we have no alternative to concluding that the very pronounced racial difference is not due to Lerner's phenodeviants, is not due to multiple homozygosity, is not even genetic, but is entirely environmental. This illustrates that some information can be obtained from outcrossing as well as from inbreeding about the effects of rare deleterious genes.

ABSTRACT*

The genetic load in man has four principal components. The *mutation load* is due to genes whose unfavorable effects are balanced by recurrent mutation. The *segregation load* is due to genes maintained by selective mechanisms (usually heterozygote advantage) independent of the mutation rate. The *incompatibility*

* This abstract is not a summary of Dr. Morton's lecture. His presentation at the conference covered only part of the ground mapped out in his original abstract. We have obtained Dr. Morton's permission to print this abstract, since it is specifically referred to in Prof. Haldane's discussion (see pp. 243-244). ED.

15 Neel, J. V., A study of major congenital defects in Japanese infants, *Am. J. Human Gen.*, *10*, 1958, 398–445.

load is due to mother-child antigenic incompatibility. The *substitution load* is due to transient polymorphism for genes that are being eliminated from the population by selection. Gametic selection, meiotic drive, and possibly other causes must contribute to the genetic load, but these are believed to be less important sources of genetic variability than the mutation, segregation, incompatibility, and substitution loads. According to one school, consanguineous marriages are the ideal device to study the mutation load, the basic tool being provided by the theory of lethal and detrimental equivalents. This provides estimates of carrier frequencies and mutation rates and purports to demonstrate by several methods that the increase of morbidity with low levels of inbreeding is due to a mutation load. There is no equally powerful method for studying the other components of the genetic load. Even if these do not contribute appreciably to inbreeding effects at low levels of inbreeding, there are theoretical reasons to suppose that they may be responsible for a large fraction of mortality and morbidity in randomly mating populations. We believe that segregation analysis combined with mortality and fertility data is the method of choice for studying segregation and incompatibility loads. The basis, results, and uncertainties of genetic loads in human populations will be discussed.

H. M. SLATIS

Problems in the Study of Consanguinity*

Part of the introduction to my paper was given by Dr. Morton, who pointed out that it is extremely important to study consanguinity, since cousin marriages give an idea of the current mutational load in man. They cannot give much of an idea of the genetic history of man unless studied for another couple of millennia to see what will happen, as we cannot really reconstruct the past. At present in Israel there are consanguinity studies under way, and what I shall do, in part, is to discuss many of the other studies with reference to what might be found in Israel and why this work might be done better here than elsewhere.

The use of cousin marriages for an understanding of gene frequencies in man goes back about 40 years but was greatly improved by Prof. Haldane's work of 25 years ago, which put it on a mathematical basis.[1,2] The rules for change of gene

* This work was performed under the auspices of the U.S. Atomic Energy Commission.

1 Bedichek, S., and Haldane, J. B. S., A search for autosomal recessive lethals in man , *Ann. Eug.*, *8*, 1938, 245-254.

2 Haldane, J. B. S., The estimation of the frequencies of recessive conditions in man, *Ann. Eug.*, *8*, 1938, 255-262.

frequency with inbreeding were distinctly set forth at that time, but Prof. Haldane[3] did it on a simple genetic system. He was thinking of genes that come into the population by mutation and go out by selection with no effect in the heterozygote. We call these good genes, because they are good to study, although they are not good to have.

Muller,[4] in a remarkable paper in 1950, dealt with the number of recessive genes each of us might be carrying—"our load of mutations"—but he did not refer to good genes. Muller was discussing bad genes because he felt that the bulk of the selection involved would be against the heterozygote, not against the homozygote. I began thinking about this problem and later published an estimate of the number of good genes the average person might be carrying, using data from cousin marriages.[5] This was soon followed by the work of Morton, Crow, and Muller,[6] who discussed bad genes again. They made one very distinct improvement over previous studies: they pointed out that one could estimate the number of deleterious genes that were being carried by plotting the coefficient of inbreeding in one direction on a graph and some effect (such as the frequency of death in infancy) in the other direction. The resulting line of best fit, extrapolated to a completely inbred individual, can be interpreted as indicating a value equal to the number of genes causing the condition under observation that an average person carries.

Imagine a simple pedigree of the marriage of first cousins. The common grandparents, let us say, at some locus A carried A_1A_2 and A_3A_4. The homozygosity expected in a child of the first cousins would be 1/64 for A_1, 1/64 for A_2, and so on. The sum of that has been called F,[7] which is a coefficient of inbreeding, and here it has a value of 1/16. If we are interested in rare recessive lethal genes, we are not interested in A_1, A_2, A_3, and A_4 but perhaps in only one of them, let us say in A_2. For some other locus, B, perhaps the grandparent not carrying A_2 was a heterozygote for an allele, B_4, which also results in a rare condition when homozygous. It can easily be calculated that the chance that these rare genes will be homozygous in the children of first cousins will be 1/64 for each, or a total of 1/32, and this is the basis for a new index of inbreeding called "little el," *ll*, named for the term that we normally use for a recessive lethal allele.[8] In human genetics up to now, people have had essentially no use for *ll*, but in the material presented here by Dr.

3 Haldane, J. B. S., The spread of harmful autosomal recessive genes in human populations, *Ann. Eug.*, *9*, 1939, 232-237.
4 Muller, H. J., Our load of mutations, *Am. J. Human Gen.*, *2*, 1950, 111-176.
5 Slatis, H. M., A method of estimating the frequency of abnormal recessive genes in man, *Am. J. Human Gen.*, *6*, 1954, 412-418.
6 Morton, N. E., Crow, J. F., and Muller, H. J., An estimate of the mutational damage in man from data on consanguineous marriages, *Proc. Nat. Acad. Sc.*, *42*, 1956, 855-863.
7 Wright, S., Systems of mating. I. The biometric relations between parent and offspring, *Genetics*, 6, 1921, 111-123.
8 Slatis, H. M., An analysis of inbreeding in the European bison, *Genetics*, *45*, 1960, 275-287.

Tanaka (p. 173) and in the material in the exhibit on the Jews from Cochin (p. 353), *ll* is of interest.

Figure 48 shows a pedigree that can be duplicated in the exhibit. This concerns a couple with three children. Their eldest daughter's daughter married their son: an uncle-niece marriage. A child born of that marriage has married somebody who is her first cousin on her father's side and her first cousin once removed on her mother's side. Here, *F* is 0.0937. Half of *F*, 0.0469, is the usual estimate of inbreeding that one uses in calculating the number of recessive genes that cause a given effect.

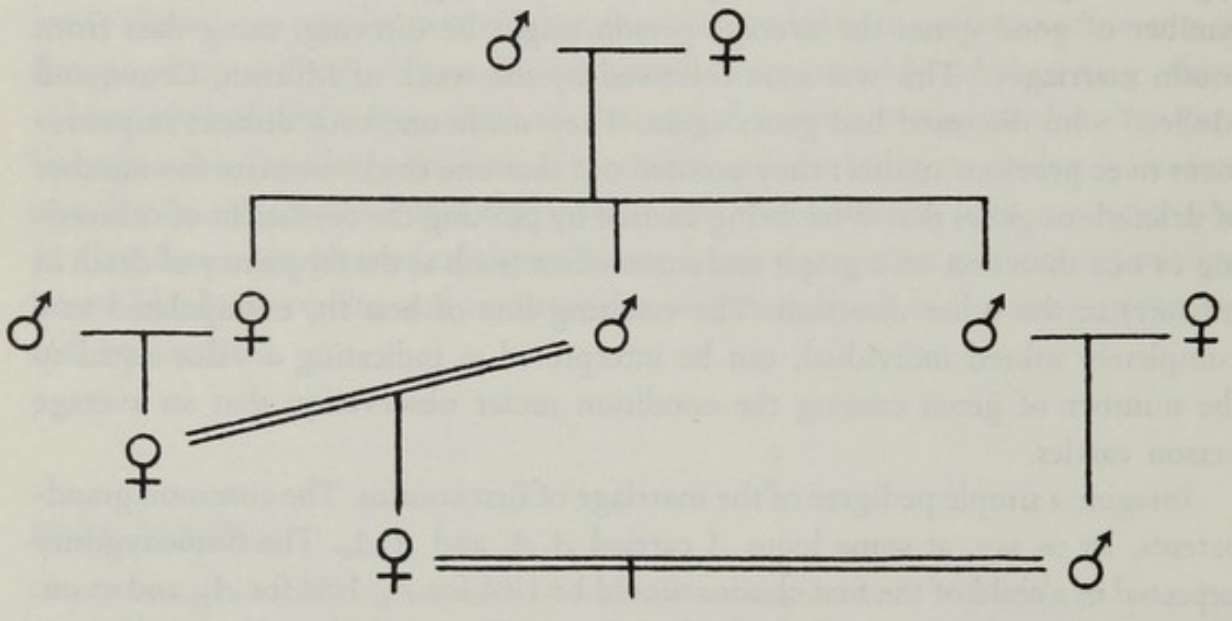


FIG. 48. Pedigree of a highly inbred marriage.

However, for these calculations the real value of inbreeding may be *ll*, which is half of *F* when there is no complication in the pedigree—that is, when no ancestors are inbred. But in Figure 48, *ll* is 0.0403, which differs from half of *F* by 16 percent. The difference between *F* and *ll* is related to a difference between the two major theories that explain the disadvantage that is often observed in inbred individuals. *F* describes the homozygosity that is due to inbreeding. Therefore, if inbreeding is assumed to be proportional to *F*, it is also assumed that the effects of inbreeding are due to a loss of heterozygosity. On the contrary, *ll* defines the homozygosity that is due to inbreeding taking account of the fact that inbred ancestors would not have been homozygous for lethal genes. If inbreeding is assumed to be proportional to *ll*, it is also assumed that the major bad effects of inbreeding are produced by the action of recessive lethal genes that have a high degree of penetrance. I shall leave this point to go on to a discussion of the findings that have been made in the studies of cousin marriages, and I shall come back to the use of inbreeding indexes at a later time.

To do cousin-marriage studies, one goes to married couples, finds out whether or not there have been children, and then investigates the health of the progeny, starting with the loss of children before birth. Miscarriage is the term I am using.

It is the common but not the preferred medical term. There will be a total of so-and-so many conceptions observed and some smaller number of these will have miscarried, giving a percentage. A similar percentage is derived from the controls. The difference between these percentages allows the computation of the gene equivalents carried by the average person and that will result in this condition when homozygous. This is then done for each subsequent step in development: stillbirth, neonatal death, death during childhood, and, finally, for the presence of abnormalities.

There is the possibility that there is a loss of conceptions even before a woman knows she is pregnant, and the question I had asked was: How about the interval between marriage and the birth of the first child? If there is some loss in cousin marriages because of early-acting lethals, there should be a lengthening of this interval. It did not turn out that way. In our United States material,[9] the cousins had their children five or six months before the controls and, similarly, the next child came earlier. There is a reason for this. The cousins marry later and therefore want their children sooner after marriage. In the consanguineous marriages, the men were 29, the women almost 25 years old, on the average. In the control marriages, the men were 27, the women almost 23. It is easy to understand why things appeared to go wrong in our study.

Schull[10] published data from Japan that can be used for a similar study. It is simplest to omit the small groups of first cousins once removed and second cousins, and to concentrate on analysis of the first-cousin marriages and the controls. The observations are limited to fertile marriages and were made when the woman registered herself as being pregnant. When 50 percent of the control women had registered as pregnant, about eight months after the beginning of cohabitation, only about 44 percent of the consanguineously married women had also registered. This 6-percent difference suggests about $3\frac{1}{2}$ genes per person that kill zygotes in the early stages of development. That is an estimate with a good chance of being at least 100 percent wrong. The estimate is dependent in large part on one's theories of why all women do not become pregnant in the first few months of marriage (in societies that do not limit family size). To get a reasonable estimate of the number of early lethal genes the average person carries, it would be necessary to compare the proportion of women conceiving during the first month of marriage in a population so large that a country the size of Israel would have to be divided into two groups, one half marrying first cousins and the other half marrying non-relatives.

Table I summarizes many of the findings published to date, giving data of Freire-Maia, Freire-Maia, and Quelce-Salgado[11] from Brazil, of Sutter and Ta-

9 Slatis, H. M., Reis, R. H., and Hoene, R. E., Consanguineous marriages in the Chicago region, *Am. J. Human Gen., 10,* 1958, 446–464.

10 Schull, W. J., Empirical risks in consanguineous marriages: sex ratio, malformation, and viability, *Am. J. Human Gen., 10,* 1958, 294–343.

11 Freire-Maia, N., Freire-Maia, A., and Quelce-Salgado, A., Lethal mutations in Brazilian human populations, *Nature, 189,* 1961, 80–81.

TABLE I

GENE EQUIVALENTS RESPONSIBLE FOR VARIOUS CONDITIONS AS ESTIMATED IN FIVE STUDIES

	Miscarriage	*Stillbirth*	*Neonatal death*	*Infantile and juvenile death*	*Abnormality*
Brazil	.21	.77	.	1.03*	
France		1.04	.88	2.40	
Japan	.16	.04	.31	1.74†	
Sweden	—2.35	—1.71	1.49	.70	2.58
U.S.	.60	.08	.04	1.90	2.33

* Includes neonatal deaths.
† Corrected for neonatal deaths.

bah[12] from France, of Schull[13] from Japan, of Böök[14] from Sweden, and of Slatis, Reis, and Hoene[15] from the United States. The column for miscarriage is limited to those reported by the woman as having occurred and so comes after the period discussed immediately above but, with varying definitions, grades into the following period—stillbirth. For miscarriage there is a uniformity in three of the studies but a wide discrepancy in the fourth. Until this morning, this fourth category was puzzling, but Dr. Goldschmidt (p. 186) pointed out that the average family size in Dr. Böök's material is certainly much larger than that observed in Japan or in the United States. I don't know the average family size for the Brazilian material. The Japanese data do not include the losses at the end of the first trimester and so may severely underestimate the effect of consanguinity on miscarriage. At any rate, any added loss due to consanguinity during the later months of pregnancy is relatively small.

For stillbirth data the general trend is toward small estimates of lethal equivalents. Here again, Böök's data from Sweden show a negative relation to consanguinity. Schull[16] has suggested that both this odd result and that for miscarriage in the Swedish material are really due to an accident of sampling because of the small number of women involved and the concentration of stillbirths and miscarriages in four of the control sibships. At any rate, lethal genes resulting in stillbirths must be very infrequent.

Neonatal deaths have generally been defined as deaths within the first month of life. The frequency of such deaths attributable to consanguinity appears to be high in the Swedish data, moderate in the French data, and low in the Japanese data. It should be noted that in this compilation the data for Japan exclude children born with gross abnormalities. Our United States data were based on so few cases that they do not count. I would predict that there is only a small effect of recessive genes on this stage of development.

12 Sutter, J., and Tabah, J., Effets de la consanguinité et de l'endogamie, *Population*, *7*, 1952, 249-266.
13 *Loc. cit.*
14 Böök, J. A., Genetical investigations in a north Swedish population. The offspring of first-cousin marriages, *Ann. Human Gen.*, *21*, 1957, 191-221.
15 *Loc. cit.*
16 Schull, W. J., Inbreeding effects on man, *Eug. Quart.*, *6*, 1959, 102-109.

Each of the five studies provided data on deaths during infancy and the juvenile period. The Brazilian data did not separate out the deaths occurring in the first month of life, and the Japanese data have to be corrected for the deaths observed in the neonatal period (the populations concerned in the data on neonatal death and on later death were quite different). There is general agreement among these studies that consanguinity has an effect on childhood death, but there is not much agreement on the magnitude of the effect. Most of the studies result in underestimates because the children are not observed all the way through childhood. On the other hand, there is a very slight effect in the other direction called compensation. If a family has had a child that died early, they are more likely than otherwise to have another child, as a replacement. This replacement, coming in a family segregating for a recessive condition, is likely to duplicate that condition and therefore also die of it. Indeed, in our own material[17] we had only one consanguineous family with more than four births. It was a family of six children, but with never more than four alive, and four died in childhood. Nevertheless, there would appear to be a greater error on the side of underestimating the effect of consanguinity in childhood death than on the side of overestimating it. Thus, these various estimates may be a bit low.

The two estimates of the effect of consanguinity on abnormalities of children are in such good agreement that we might suppose that both are wrong. (The figure cited for the Swedish sample was calculated from the information given by Böök[18] using the criteria for this category employed by Slatis, Reis, and Hoene.) The same errors of underestimation and overestimation seen for childhood death apply to these ailments, and here too there is an over-all tendency to underestimate the effects.

It is particularly in the analysis of childhood deaths and abnormalities that workers in Israel will be able to make a major contribution to human genetics. Heretofore, recessive conditions have not been described as being anywhere near the frequency in which they must exist. The reason for this is simply that the average physician does not consider any condition as inherited unless he can see that it has come from a parent, and a recessive condition is rarely observable in a parent. Therefore, we still have the problem of defining the reasons that cause the children of consanguineous marriages to be sicker or to be more likely to die than the children of nonconsanguineous marriages.

Table II summarizes my guesses about the average load of recessive genes or gene equivalents that results in given conditions. The term "guesses" has been used to emphasize the great uncertainty involved in this list and also to point out that these numbers constitute a personal prediction of what a large study of a modern population will find. Of the more than 9 lethal equivalents, all but the 3.5 equivalents lethal to the zygote are important to society, though, on the whole, the farther one goes down on the list, the more there is a sociological and psycho-

17 Slatis, H. M., Reis, R. H., and Hoene, R. E., *loc. cit.*
18 *Loc. cit.*

TABLE II
GUESSES ABOUT GENE EQUIVALENTS

Lethal to the zygote	3.5
Observed miscarriage	.5
Stillbirth	.1
Neonatal death	.2
Infantile and juvenile death	2.5
Abnormality	2.5
	9.3

logical significance. Therefore, from the standpoint of the community, the load is a good deal closer to 5 than to 9 lethal equivalents.

We have been discussing recessive genes and trying to find out how many there are and what effect they have upon our lives today and those of our descendants. The effect is dependent on whether the bulk of the inbreeding load is due to good genes or bad genes. Perhaps here in Israel there will be a chance to add evidence on this question through the use of *ll*. Almost anywhere else, it does not make any difference whether you use half of *F* or *ll*, but since in Israel one can find instances of consanguineous marriages involving inbred persons, there will be a difference between these two inbreeding indexes.

The traditional method of analysis has been to compare marriages between first cousins, between cousins of more distant degree, and between unrelated persons. With an intensive study here, one should be able to find adequate numbers of marriages between relatives with inbred ancestors. The advantage accruing from the use of these highly inbred individuals might well justify the work of collecting these rare pedigrees.

As has been noted, the analysis of inbreeding data compares the frequency of a condition at various levels of inbreeding. If inbred individuals are affected more often than outbred individuals, it is assumed that the difference between the groups reflects the homozygosity of the inbred individuals. When there is more than one level of consanguinity, it is reasonable to expect that there should be a direct relationship between the amount of inbreeding and the effect due to inbreeding. Since *F* and *ll* result in distinctly different relationships between the various types of close inbreeding, one might investigate the goodness of fit of the observations to a straight line. If the relationship between *F* and some effect of inbreeding is closer than that between *ll* and the same effect, then one would have evidence that the genetic consequences of inbreeding occur because of the loss of heterozygosity. In the event of the converse, with *ll* more closely related to the magnitude of an effect than is *F*, the evidence would point to simple recessive genes as the cause of the bad effects of inbreeding. Incidentally, if one suspects that persons who marry relatives differ from the average, one could follow the lead of Morton, Crow, and Muller[19] and use somewhat less closely related families to help establish the trend

19 *Loc. cit.*

of the line, omitting a control of nonconsanguineous families. The comparisons, in this way, would be limited to consanguineous marriages of differing degree and thus would minimize the psychological effects attributable to consanguinity.

One can assume that the deleterious effects attributable to consanguinity should be proportional to the degree of inbreeding. With a large body of data, there may be a distinct difference in the correlation between the frequency of abnormalities and the level of inbreeding according to whether inbreeding is defined by *F* or by *ll*. In the interpretation of inbreeding effects as described by *ll*, there is the assumption that almost all of these recessive genes are good genes—that is, they have high penetrance and no effect in the heterozygote. The end result of this analysis would be that the calculation of gene equivalents will be similar to the actual number of loci involved. Measurements of inbreeding using *F* imply that homozygosity as such is bad for the individual and that it is bad genes that cause the children of consanguineous couples to have a substandard health level. And so, if I were studying cousin marriages in Israel, I would try working this out to see what contribution could be made to our understanding of the mechanism of gene action.

STERN: Thank you, Dr. Slatis. We now have the pleasure of listening to Prof. Haldane.

J. B. S. HALDANE

The Concentration of Rare Recessive Genes in the Past and in Modern Times

Dr. Stern, ladies and gentlemen: I owe you several apologies. Kind reference has been made to some contributions I made to this subject some 25 years ago. But I have deserted it to a large extent, and I have not followed a lot of the recent work. For that I am no doubt to blame. But if I had been less in demand for one purpose or another during the past four days, I could have devoted more time to discussions of my colleagues' demonstrations, and, in particular, I could have assimilated, as I have not done, the exhibits (see pp. 251-355). But I have had only about two and a half hours in which to look at them, and I should have needed about fifteen.

Several papers in this discussion have been devoted to genetic load. Let me say that I dislike this phrase. Few or no human deaths or sterilities are due to one cause only. And in particular I want to criticize Dr. Morton's summary as it appears in the abstract book much more than the paper which he actually read, with which I was considerably in agreement. But I hope he will forgive me if I criticize the

abstract. Perhaps the reason why he did diverge from it was because he himself had seen that there was a certain inconsistency in it.

Let me take an example. It appears probable that the high frequency of the Rh-negative gene *(d)* in Western Europeans may be due to crossing between a population which had a majority of *d* genes, such as the modern Basques and the people of Wallis in Switzerland, and immigrants from the East with a large majority of Rh-positive *D* genes. And it seems at least likely that *d* is being eliminated, or at least reduced considerably, as a result of incompatibility. If this is so, the deaths from neonatal jaundice and the like due to this cause contribute both to the substitution load, as Dr. Morton calls it, and to the incompatibility load. The gene is disappearing under natural selection. Therefore it contributes to the substitution load. It is eliminated owing to incompatibility. Therefore it contributes to the incompatibility load.

In other cases, again, incompatibility may be balanced by advantage of heterozygotes, and it seems likely to be so at the ABO locus. If so, the deaths due to incompatibility are included both in the incompatibility load and in the segregation load. If overlapping loads are to be considered, I should certainly like to add another load to the list. I hate to complicate the terminology but I would suggest we might call it the "displacement" load or, if you like, a "migration" load, but I think I prefer the displacement load. This load is due to the fact that the existing genotypes in a population are not in general in their optimal environments. If malaria still exists in some regions of a country, as it still does in some regions of India, even though it is pretty well eradicated in Israel, many deaths could be avoided if all the persons with G6PD deficiency could be transferred to these malaria areas in exchange for persons who are not adapted genetically to resist malaria.

Now, when we turn to plant ecology, that becomes quite important. If you have a rather immobile plant, such as *Plantago maritima,* you will get different local races within a few hundred yards of one another adapted to the local soil and other conditions, whereas if you have a plant with mobile seeds you do not get anything of the kind. There is, therefore, for the mobile plant a considerable displacement load or whatever you choose to call it.

I would also beg to question Dr. Freire-Maia's terminology, though, of course, I agree with his conclusions. I am not certain that the genes responsible for the increased early mortality in the progeny of consanguineous marriages in Brazil belong, as he says, to the "mutational load." There are two other possibilities which, I believe, have to be considered. On the one hand, these rare and lethal or sublethal recessive genes, some of them, could be ancient genes which were quite normal in the human race, let us say in early paleolithic times, but against the existing genetic background and in the existing environment are now more or less lethal. That is to say, the deaths due to those genes are part of the substitutional load.

It is some fifty years since Pearson pointed out the extraordinary slowness with which lethal recessive genes are eliminated, and I believe we have to consider the possibility that some of our detrimentals are part of the substitutional load. They have become sublethal because other genes have evolved so much. I think it is highly possible that if a paleolithic man or woman from 500,000 years ago could be resurrected and could be mated with a modern person, one would find very considerable lethality in the second generation. And I want to suggest that some of the rarer lethal genes may be residues and that the effect of them may be part of the substitutional load.

There is still another possibility which is opened up by Dr. Dobzhansky that they could be what Dobzhansky calls "synthetic lethals." I think synthetic lethals are much less likely to occur in human populations with large chromosome numbers than in Drosophila, but they may not perhaps be impossible and, if so, they might be more frequent in a group of very mixed racial origin such as the nonwhites of Brazil who have probably some white ancestry and ancestry from a good many African groups and perhaps from some South Americans.

The problem on which we are supposed to be speaking is the concentration of rare recessive genes in the past and in modern times, and this is obviously of very great interest for Israel because Israelis know a good deal more about their past than most other people. This problem is obviously far more complex than appeared to me to be the case 30 years ago, not only because I concentrated on fully recessive genes—by which, as Dr. Slatis pointed out, I was making the thing as easy for myself as possible, thereby misleading others—but for other reasons.

By a study of the children of first cousins we can obtain an estimate of the frequency with which one of their common grandparents was heterozygous for rare recessive genes. That is essentially what we are doing when we study the children of first-cousin marriages. But these common grandparents cannot be regarded as a random sample of the population in which they occur. They would disproportionately often belong to groups which are at least to some extent geographic, religious, or cultural isolates within the main population and in which natural selection following inbreeding has therefore probably lowered the frequencies of deleterious genes. It seems to me that we might perhaps ask the following questions, which could be answered at least in some populations. First, if two first cousins marry, what is the probability that their parents were also first cousins? Secondly, if two first cousins marry, what is the probability that they are also themselves second or third cousins? If those probabilities are substantially above average, then we have to make serious corrections in some of our calculations.

Now, it appears possible that these questions could be answered in Sweden and in a county like Parma, in northern Italy, where there are fairly good records going back for a considerable time. You will note that I did not go back more than four generations in the questions which I asked. I think it would be of very great value

to get an answer to that question without any reference to the pathology of the children. It may be that the correction to be made is quite unimportant. It may be more important than we think. This kind of heterogeneity in the mating system may or may not be as important as the heterogeneity in gene frequency to which our attention was drawn this morning in connection with acatalasia in Japan (pp. 176-183).

Dr. Goldschmidt and her collaborators conclude from their results (p. 184) that incompatibility may be responsible for a large fraction of prenatal mortality. It may be that the populations that they studied are somewhat exceptional in the importance of incompatibility, but even so these results are there and require comment. One would like to hear how Dr. Slatis would reply to these facts, how far such facts might modify his conclusions. It might be that if, after all, the death rate from incompatibility is as important as it certainly appears to be in Dr. Goldschmidt's data, then the load of lethals—at least of those acting prenatally—may be considerably more than Dr. Slatis believes. I should like to make another suggestion about Dr. Goldschmidt's paper. Excess of males in inbred families may be due, as I suggested, to partially sex-linked recessives, but it is highly possible that partial sex-linkage, though it certainly exists in mosquitoes, exists in humans only as a hypothesis of which I am guilty. But such an excess of males could be due to relatively rare, but not very rare, autosomal recessives with an early lethal effect on females and not on males. Such genes could be kept in being by mutation or they could be balanced either by saving the lives of heterozygotes or by an opposite effect on females. I want to put that forward only as a suggestion of the kind of rare genes for which we perhaps ought to look.

During the past few centuries inbreeding has relaxed in many peoples, and mutation rates may have changed. Certainly they may have changed in the last generation largely as a result of the existence of atomic bombs and so on, but they may have changed quite drastically as a result of changes in food habits, the inclusion in the diet, or the exclusion from the diet, of various mutagenic substances. We certainly take plenty of substances which are mutagenic for some other organisms.

Furthermore, the intensity of selection against homozygotes has diminished in pretty well all cases except those in which the homozygote may have altered or selection may even have changed direction. It is mainly our ignorance on this last point, it seems to me, that makes calculations as to past gene frequencies precarious. Nevertheless, in some cases gene frequencies can have changed only little in several centuries. If we take some of these recessive conditions on which we see data in the exhibits (pp. 251-355), the fraction of the genes eliminated by selection per generation is less than one in a hundred. That may be balanced by mutation, or mutation may be even working more rapidly. Nevertheless, I think we can then extrapolate a good long way back into the past. We can suggest, for example, that

the differences found between the Ashkenazic Jews and other Jews go back for at least 1000 years and could be, of course, explained by the incorporation of non-Jewish elements into the Ashkenazim and so on. But without a direct estimate of mutation rates and a very exact knowledge of the fitness of heterozygotes, it is impossible to calculate whether a population is or was in equilibrium.

But since equilibrium is approached far more rapidly under high than under low inbreeding, it is much more likely that equilibrium exists in highly inbred populations, such as those of southern India, than elsewhere. I stress southern India because, for example, the population of Andhra Pradesh, of which we have heard (p. 154), consists of at least 10 million persons and there are probably all together 70 million highly inbred people in southern India. In such large populations, drift will be quite unimportant. Moreover, there are relatively fewer heterozygotes and therefore the equilibrium of nearly recessive genes may perhaps be more easily determined by the mutation rates.

To conclude, we still have a very long way to go. Where there has recently been a large change in environment, as with the eradication of malaria, we can be only fairly sure that gene frequencies are now changing—and changing fairly quickly. But we are not at all sure what will have been the effect on gene frequencies of environmental changes in the past, such as the dispersion of the Jews from this country, which led, incidentally, to their urbanization at an earlier date than any other components of the European civilization. We do not really know how this early urbanization affected the gene frequencies in these Jewish populations, although we can guess fairly at the effects of progressive urbanization of Europe in the past two centuries and of the United States more recently.

I believe that the answers to our questions will be found only by intensive studies of particular genes and by intensive studies of fairly small populations, such as the Kurdish Jews, in whom a particular phenotype is probably an expression of one, and only one, genotype, whereas in Israel as a whole, let alone in the United States, it may be the expression of 5 or 50 different genotypes.

For these reasons, the intensive studies now being made in Israel, whose results or some of whose results we have seen or heard, are of the greatest value not only for Israel but for the human species as a whole. They will help us to understand not only the past of Israel but the past of mankind.

STERN: The papers are now open for discussion.

There is one component of the genetic endowment of a population which has not been mentioned in our discussions but which also may play a role in changing the frequencies of rare defect-causing genes. This component is represented by the normal alleles of these genes. It has become apparent that in a population there may exist at any one locus not only multiple mutant abnormal alleles but also multiple normal alleles. One of the early cases that shows this

phenomenon refers to the venation of the wing of *Drosophila melanogaster*.[1,2] A mutant allele for an interrupted vein, *ci*, is usually called recessive because in heterozygous combination with wild type, +, normal, uninterrupted veins are produced in most cases. It was found, however, that there are a number of wild-type isoalleles, $+^1$, $+^2$, $+^3$, etc., all leading to normal venation in homozygotes but distinguishable by their effect in heterozygotes with *ci*. Thus, at 26°C., wild-type alleles $+^1$ and $+^2$ in the combinations $+^1/ci$ and $+^2/ci$ produce normal wings but many individuals of the genotype $+^3/ci$ have interrupted wings. We thus have a series of wild-type isoalleles none of which causes abnormality by itself but some of which cause abnormality in combination with a deleterious recessive allele.

Indications for the presence of normal isoalleles in man were pointed out by Penrose some years ago.[3] There is a negative correlation between age of onset of dominant autosomal muscular dystrophy in parents and children. This can be interpreted in terms of different normal alleles $+^1$, $+^2$, etc., which in combination with the mutant allele, *M*, lead to different ages of onset. If, for instance, the heterozygote $M/+^1$ has early onset, whereas $M/+^2$ has late onset, then a marriage of the type $M/+^1 \times +^2/+^2$ will produce $M/+^2$ offspring, and a marriage of the type $M/+^2 \times +^1/+^1$ will produce $M/+^1$ offspring, in each case presenting a shift of age of onset between generations. A similar argument for different normal alleles has been advanced by Renwick,[4] who suggested that the dominant allele *P* for the nail-patella syndrome in the combination $P/+^1$ may lead to relatively slight defects whereas $P/+^2$ individuals are more severely defective. Still another case of fundamentally similar type has been suggested by Itano[5] for hemoglobin synthesis.

These examples show that the selective values of heterozygotes do not depend solely on the rare mutant alleles. Whenever there is a polymorphism for normal alleles in populations, selective forces which determine the frequency of the rare allele will vary according to the kinds and the proportions of the normal alleles. These proportions again are likely to be subject to selective influences depending upon the properties of the different normal homozygotes and the heterozygotes between the normal alleles themselves as well as on the frequencies of the different heterozygotes between normal and abnormal alleles. It is possible that some of the differences between populations in the frequencies

1 Stern, C., and Schaeffer, E. W., On wild-type isoalleles in Drosophila melanogaster, *Proc. Nat. Acad. Sc.*, *29*, 1943, 361-367.

2 Hochman, B., Competition between wild-type isoalleles in experimental populations of Drosophila melanogaster, *Genetics*, *43*, 1958, 101-121.

3 Penrose, L. S., The problem of anticipation in pedigrees of dystrophia myotonica, *Ann. Eug.*, *14*, 1948, 125-132.

4 Renwick, J. H., Nail-patella syndrome: evidence for modification by alleles at the main locus, *Ann. Human Gen.*, *21*, 1956, 159-169.

5 Itano, H. A., Qualitative and quantitative control of adult hemoglobin synthesis—a multiple-allele hypothesis. *Am. J. Human Gen.*, *5*, 1952, 34-45.

of the rare alleles are the result of differences in normal alleles. This hypothesis may become subject to test when methods become available to distinguish different normal isoalleles.

Our president has agreed to make the closing remarks for the last meeting of this conference.

J. B. S. HALDANE

Closing Remarks

I am genuinely sorry to close this conference. I should like to have heard a great deal more from a number of the speakers and from a number of those who have not spoken but whose work has been demonstrated to us to some extent in the exhibit (see pp. 251-355). Above all, I should like to have been able to spend another week or two in seeing some of the actual subjects on which they are working and the methods they are employing.

But I can say this: I can tell those who have organized this conference—and those who so generously supported it, including representatives of the Israeli government and of various American organizations—I can tell them that this meeting has been a success. It is possible that it has not come up to the expectations of those who hoped that it would throw light on the history of the people who are now gathering together again in history. It certainly has illuminated many important facts, but I think that most of the results thus far obtained are capable of several historical interpretations. That they mean something is quite certain. Just what they mean, I do not know.

I would like someone in Israel to do a paper comparing the range of frequencies of various genes found in the diverse Jewish populations which are now converging on Israel—true to the vision of the Psalmist: "Turn us again, O Lord, like as a river in the South." Those who are being turned again—I would like a little diagram to show how the range of frequencies of different characters in them compares with those in the world as a whole. The conference exhibit shows such comparisons for one or two characters. But I believe that it would be of very considerable interest to include many others. It would show perhaps that some characters may be regarded as having been unchanged for a long time, while others—such as, for example, the genes responsible for resistance to malaria—are of comparatively recent origin. I hope this will be done. I fully realize that the time has not come to do it on so large a scale as we might like.

But if the results of this conference have not fulfilled all the hopes put into it from that point of view, they have most certainly been of value in two quite different ways. First, they have given rise to presentation of papers and discussions on a very high level. Of course, we visitors pat ourselves on the back and we say:

"We are the men whom the king delighteth to honor, who have been invited to the holy hill of Zion" and that is why we are so good. I am not sure that that is the whole story. I think that the level of the contributions made from Israel put us on our mettle. We felt that if this is the kind of work that is being done here, we really must try to show our best side—not to be inaccurate, not to be too uncritical.

We foreigners will go back with a most lively recollection of the work in human genetics that is being done in Israel. I can wish only that we had had more time to see something of the agricultural work that is being done. To a very large extent, the wonderful sights that we have seen, especially at the *kibbutzim,* have been due not to genetic improvement but to decent treatment of animals and plants. And they have shown me, at any rate, that in the climate of the Jordan Valley, which is not unlike that of many of the hotter parts of India, things are possible which were believed to be impossible in such a climate.

I am sorry to digress, but I should like to say as a biologist how enormously I was impressed by the agriculture in this very hot region and, of course, the beginnings of agriculture in the very dry region of the Negev, which I hope "will blossom like a rose" within the next years.

I want in the name of all the foreign guests to thank our hosts most warmly. I am sure that many of us will come back to Israel and spend somewhat longer times than we have. It is all very well to read about Israel. It is all very well to see photographs of *kibbutzim,* to see photographs of famous historic sites and so on. But the reality surpassed at least my expectations.

EXHIBIT SECTION

The Genetics of Israel's Populations

NOTE: For a detailed listing of the contents see page xviii.

IT IS THE VARIETY of human populations settled in the comparatively small area of Israel that has given the stimulus to most of the research projects that are summarized in the following pages. The results of the various investigations, in so far as they are available to date, are presented in graphs and tables. It is inherent in the nature of a compilation of this type that it includes investigations differing in scope and breadth—that extensive data have accumulated in certain fields whereas others have merely been mapped out for future exploration. This synopsis of the genetics of Israel's populations is thus neither comprehensive nor complete.

The various research groups investigating the reassembled diaspora began without being directed by a master plan and, although common interests soon ensured contacts and coordination, a lack of uniformity may be felt in certain technical aspects, the most important of which is the classification of the populations studied.

Although an effort has been made to standardize the group designations throughout the contributions of this section, it has succeeded only in part because of the different methods by which the data had been assembled.

Ideally, the classification of the Jewish communities should be based on their short-range phylogeny. This could be achieved if complete historical data were available on the radiations of these groups from Ancient Palestine into the countries of the diaspora and on the ramifications of the main migration lines. Alternatively it may seem safest to disregard the sketchy historical information altogether and to group the communities merely by those continents and countries which were their last station in the diaspora. Indeed, the classification of the Jewish communities in the present volume is mainly based on the most recent pattern of their geographical distribution. This principle was abandoned in only a few cases in which two Jewish congregations (the Sephardim and the Ashkenazim) had preserved their separate identities by traditional barriers in spite of partially overlapping geographical distributions.

Any attempt to condense the history of the Jewish communities, facts and conjectures, into the space available here would be futile. The following brief account of the re-entry of various Jewish groups into Israel should serve merely as a directory to the terminology with which the population geneticist in this country is faced.

The dispersal of the Jews and of the Jewish religion from Ancient Palestine (Israel) is assumed to have

taken place in three major waves: the Assyrian Exile—721 B.C.; the Babylonian Exile—586 B.C.; and—the Roman Exile, following the destruction of the Second Temple in A.D. 70. These migrations resulted in the foundation of Jewish colonies in Mesopotamia and other countries of the Near East, around the Mediterranean shores, and in central and western Europe. In the late Middle Ages it became customary to refer to the diaspora of central and western Europe as the Ashkenazic group of Jews.

During the Middle Ages migrations of individuals or of small groups ensured some measure of cultural contact between the various Jewish colonies and also provided for a certain amount of gene flow between them. A large-scale shift of the Jewish populations occurred at the dawn of the Renaissance as the consequence of the expulsion of the Jews from Spain in 1492. The exiled Spanish Jews, who called themselves Sephardim, settled in the Netherlands, Britain, France, Italy, and the Balkan countries as well as in North and South America. In many European countries Sephardic and Ashkenazic congregations came to exist side by side. The Sephardim are assumed to have contributed some reinforcements to the Jewish colonies of North Africa, the Turkish peninsula, Syria, and Palestine. A few of them may have reached Mesopotamia and possibly other countries of the Near East.

After the Roman Exile, throughout the Middle Ages, Palestine was never completely deserted by the Jews. Small congregations of Jews existed in various places, notably in Jerusalem, Hebron, Safad, and Tiberias. Although individual immigrants of nearly all communities arrived during each century, the Sephardim were the largest single Jewish group in the Holy Land after the expulsion from Spain. Nevertheless, until the second half of the nineteenth century the Jews of Palestine remained restricted in number.

Starting with the end of the eighteenth century first under the Turkish regime and after World War I under the British Mandate, the Jews began flocking back into Israel in successively larger waves of immigration. Although the majority of these "earlier" immigrants were Ashkenazim, substantial numbers of Sephardim and of Jews from Iraq, Kurdistan, Persia, Yemen, Cochin, Turkey, Syria, and North Africa also entered Israel during this period.

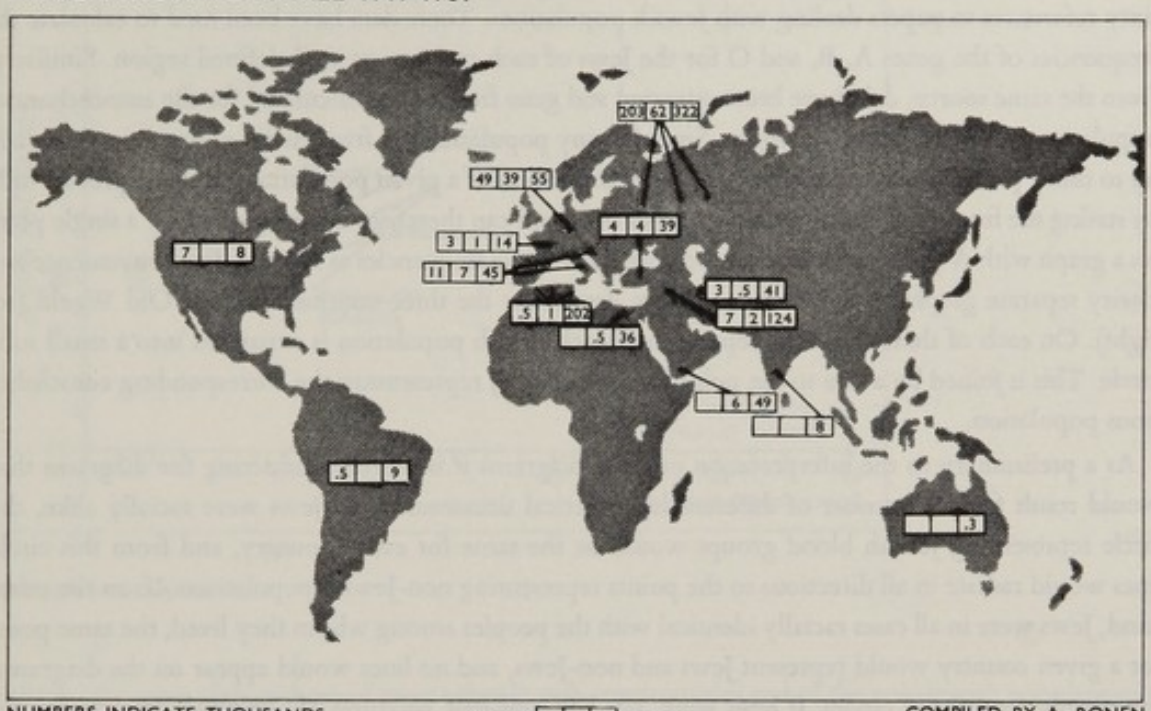
After the establishment of the state of Israel in 1948, a million Jews from various countries arrived. The map indicates the composition of the three most recent immigrant waves. The present state of Israel's populations is summarized in the diagram.

The Jewish Israeli-born, who already constitute more than 30 percent of today's Jewish population, present an ever-growing problem to the field worker in genetic anthropology. Many official statistics and medical files contain no further specification of the origin of these individuals, although by thorough personal interviews the ethnic affiliation of their parents can still be elucidated in a large proportion of cases.

The non-Jewish Israel-born, among whom the Arabs and Druses are the most important, can be easily grouped into further subunits according to their traditions and their tribal affiliations. The various urban, rural, and seminomadic groups of Moslem and Christian Arabs as well as the village congregations of Druses constitute a series of genetic isolates with varied structure. The inclusion of all these communities in comparative population studies is attractive in many ways, but in particular in view of their isolate character and of the presumed ethnic affinities of some of them to the Jews of Ancient Palestine.*

* The help of Dr. S. Ettinger, who checked the historical data presented in this outline, is gratefully acknowledged.

IMMIGRATION TO ISRAEL 1919-1961

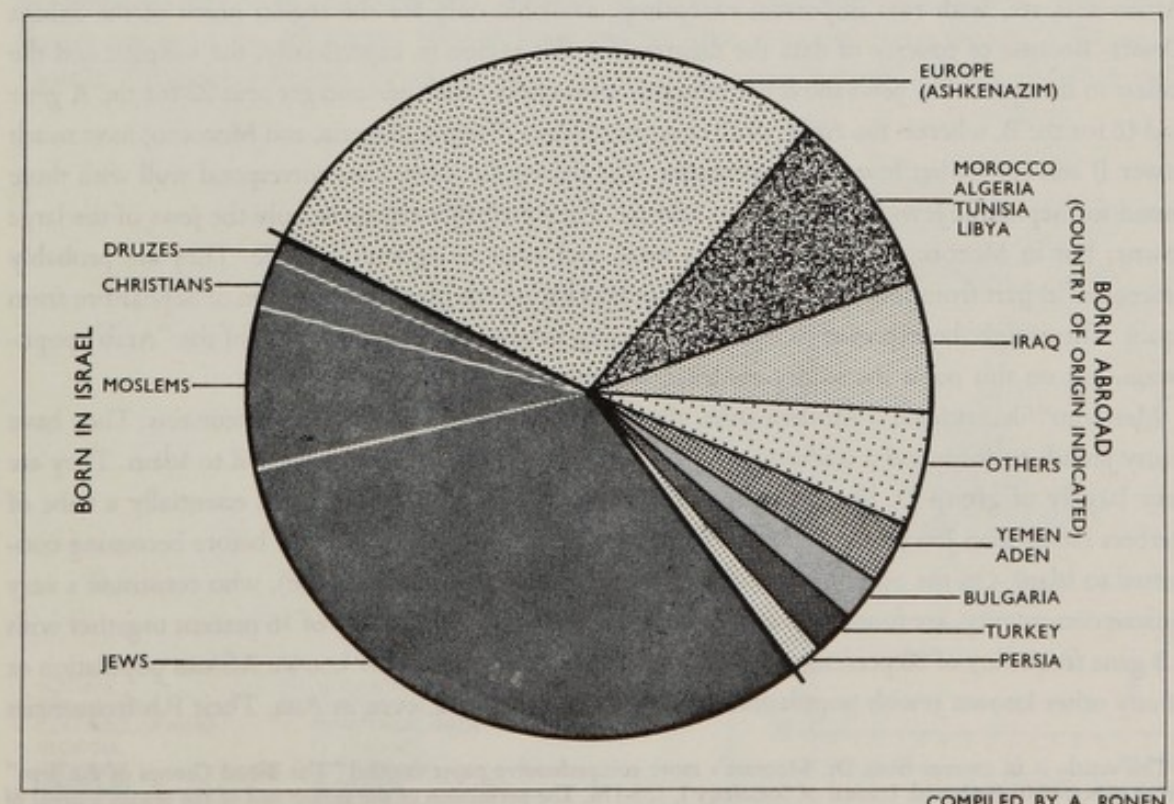


NUMBERS INDICATE THOUSANDS OF IMMIGRANTS

1919-1938 | 1939-1947 | 1948-1961

COMPILED BY A. RONEN

COMPOSITION OF ISRAEL'S POPULATION BY COUNTRY OF BIRTH



COMPILED BY A. RONEN

A RECENT COMPILATION[179] of all available records of ABO blood group surveys contains more than sixty references to papers dealing with Jewish populations. These data have been used to calculate the frequencies of the genes A, B, and O for the Jews of each country or well-defined region. Similarly, from the same source, data have been extracted and gene frequencies calculated for the autochthonous populations of each country or region. Since for any population the frequencies of the three genes add up to unity (or their percentages to 100), the composition of a given population can be expressed fully by stating the frequencies of the A and B genes only and can therefore be represented by a single point on a graph with A gene frequencies as ordinate and B gene frequencies as abscissa. For convenience and clarity separate graphs of this kind have been drawn for the three continents of the Old World (see right). On each of these the point representing each Jewish population is expanded into a small solid circle. This is joined by a line to the point (without circle) representing the corresponding autochthonous population.

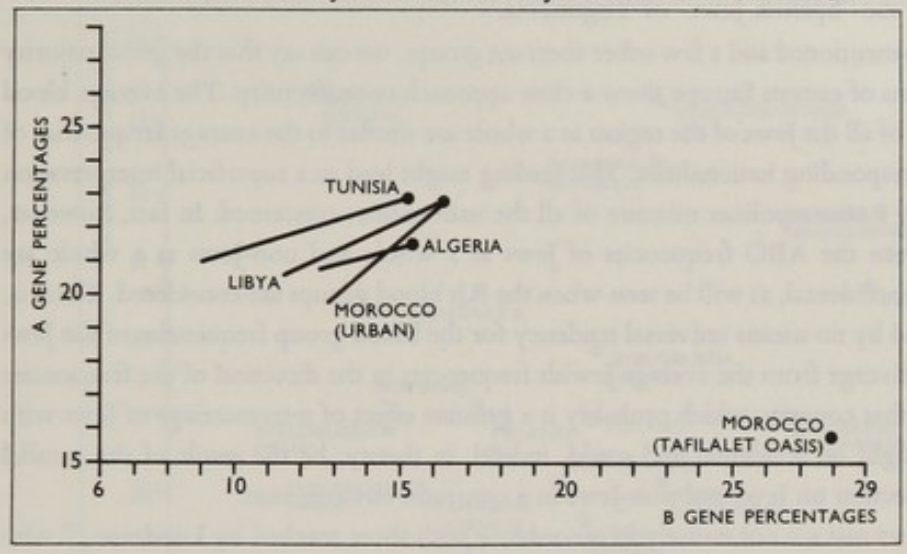
As a preliminary to the interpretation of these diagrams it is worth considering the diagrams that would result from a number of different hypothetical situations. If all Jews were racially alike, the circle representing Jewish blood groups would be the same for every country, and from this circle lines would radiate in all directions to the points representing non-Jewish populations. If, on the other hand, Jews were in all cases racially identical with the peoples among whom they lived, the same point for a given country would represent Jews and non-Jews, and no lines would appear on the diagrams, but simply a scatter of circles. If Jews were, say, half-and-half mixtures of "original" Jews and autochthones, the circles representing actual Jewish populations would be distributed irregularly around the point representing "original" Jews, and the lines would radiate outward in many directions toward the points representing pure autochthones, but if the lines were all extended inward they would meet at a point representing "original" Jews.

In fact, none of the diagrams represents anything like any of these ideal conditions. In the case of Africa data are, with two important exceptions, available only for the region north of the Sahara Desert. Because of paucity of data the diagram for this region is, superficially, the simplest and the easiest to interpret. The Jews show considerable uniformity, with percentages near 22 for the A gene and 16 for the B, whereas the Arabs of all countries (Libya, Tunisia, Algeria, and Morocco) have much lower B and somewhat lower A percentages. The figures for these Jews correspond well with those found for Sephardic Jews in Israel and in Europe. They probably represent only the Jews of the large towns; but in Morocco many Jews live a rural, and even an agricultural, life. They are probably descended in part from Jewish proselytes of a period before the great immigration of Sephardim from Spain. They might be expected to have blood group frequencies nearer to those of the "Arab" population, but on this point the scanty evidence is somewhat conflicting.

Messerlin[171] has studied a Moslem tribe, the Aït Slimane of the Haut Atlas Mountains. They have many Jewish customs and a tradition that they were Jews who became converted to Islam. They are very largely of group O, like the neighboring Berbers, and thus appear to be essentially a tribe of Berbers rather than Jewish immigrants, but they may have embraced Judaism before becoming converted to Islam. On the other hand, the Jews of the Tafilalet Oasis (see figure), who constitute a very ancient community, are found by Lévêque[156] to have an A gene frequency of 16 percent together with a B gene frequency of 28 percent, which is higher than that of any other known African population or of any other known Jewish population in any part of the world, even in Asia. Their Rh frequencies

* This article is an excerpt from Dr. Mourant's more comprehensive paper entitled "The Blood Groups of the Jews" which appeared in the Jewish Journal of Sociology I, 155-176. The permission of the author and of the Jewish Journal of Sociology to reprint this excerpt is gratefully acknowledged.

ABO BLOOD GROUPS IN JEWS AND NON-JEWS OF NORTH AFRICA



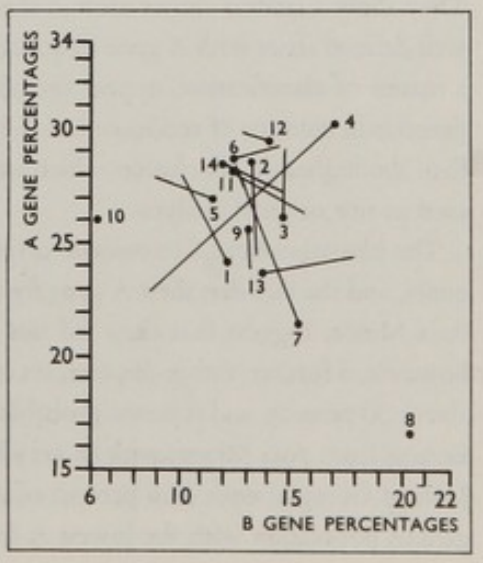
FOR EXPLANATION SEE TEXT

fall into the same class as those of most other Jewish communities and of the non-Jewish populations of the Mediterranean area and southwest Asia, including India.

The Falasha of Ethiopia,[4] however, with 24 percent of A genes and 10 percent of B genes, differ relatively little in their blood group frequencies from other peoples of Ethiopia.

The diagram yielded by the Jews of Europe (see below) is a much more untidy one, but certain regularities can be seen. The Jews of Hungary, Poland, Ukraine, and White Russia cluster around the percentages A, 28.5; B, 12.5. Not very different are those of Germany and Romania. Very similar figures are given by Ashkenazic Jews in Israel and by Jews, presumably from eastern Europe, in Canada. The Jews of Austria, Czechoslovakia, Lithuania, and Great Russia have rather fewer A genes

ABO BLOOD GROUPS IN JEWS AND NON-JEWS OF EUROPE



1 AUSTRIA
2 BYELORUSSIA
3 CZECHOSLOVAKIA
4 GEORGIA
5 GERMANY
6 HUNGARY
7 JUGOSLAVIA
8 KARAITES
9 LITHUANIA
10 NETHERLANDS
11 POLAND
12 ROMANIA
13 RUSSIA
14 UKRAINE

(about 25 percent) and about 13 percent of B, tending toward the figures for the Sephardim, which are typically shown by the "Spanish Jews" of Yugoslavia.

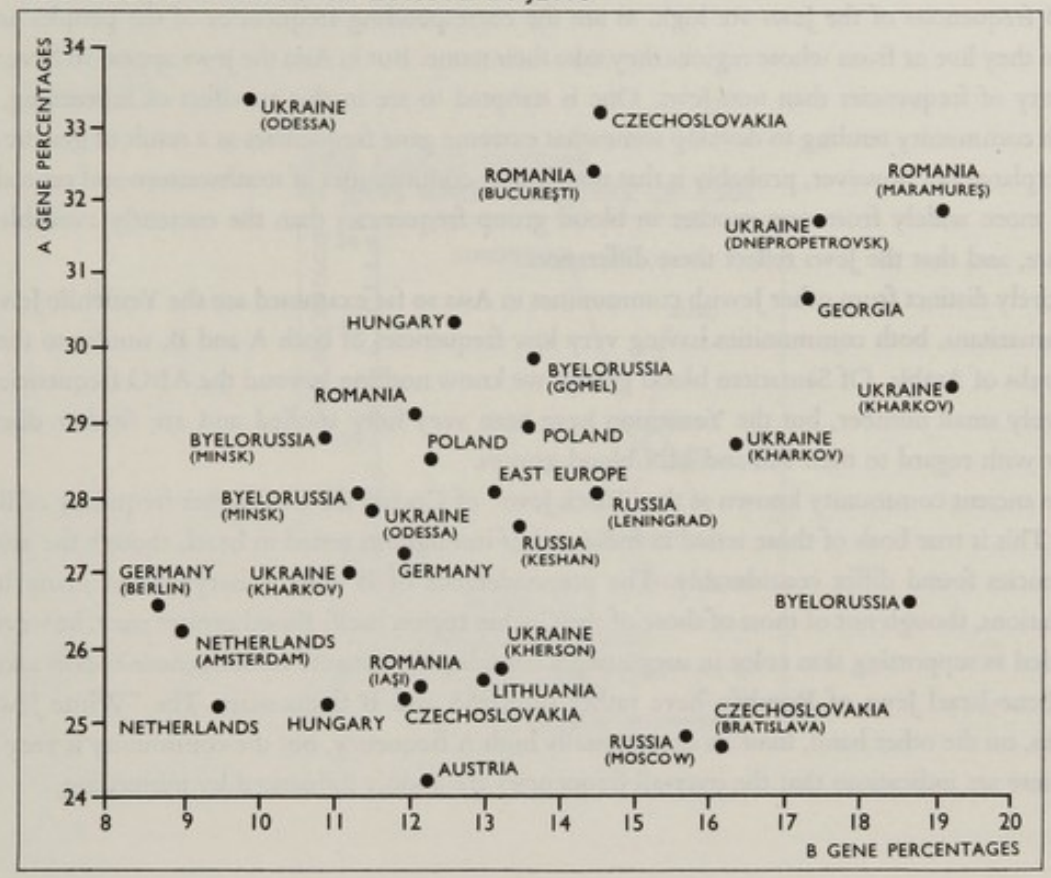
Disregarding the last-mentioned and a few other aberrant groups, we can say that the great majority of the Jewish populations of eastern Europe show a close approach to uniformity. The average blood group gene frequencies of all the Jews of the region as a whole are similar to the average frequencies of all the non-Jews of corresponding nationalities. This finding might lead to a superficial interpretation that the Jews are simply a cosmopolitan mixture of all the nationalities concerned. In fact, however, the resemblances between the ABO frequencies of Jews as a whole and non-Jews as a whole are deceptive and probably accidental, as will be seen when the Rh blood groups are considered. There is, nevertheless, a slight and by no means universal tendency for the blood group frequencies of the Jews in any one country to diverge from the average Jewish frequencies in the direction of the frequencies shown by non-Jews in that country, which probably is a genuine effect of intermarriage of Jews with non-Jews, though it might be accidental and could, indeed, in theory, be the result of the parallel operation of natural selection on Jews and non-Jews in a common environment.

The conclusions just set out are not entirely in accordance with those reached by Lundman,[157] who in his comprehensive survey of Jewish blood groups uses a somewhat different approach, and whose paper came into my hands only when my analysis of the data was already in progress. I considered that, with the relatively large amount of data available, regional averages of blood group frequencies would be more likely to reveal any general patterns than would the results of the individual surveys. Lundman, on the other hand, lists separately the results of these surveys, and in the case of the Ashkenazim he concludes that there are two main groups, an eastern with average gene frequencies A, 28.5 percent, B, 15.0 percent, and a western with A, 26.5 percent and B, 12.5 percent. He further concludes provisionally that the eastern group entered Europe via Asia Minor and Poland, and the western via Rome and southern Germany. In view of this suggestion and of the undoubted importance of Rome as an early center of dispersal of Jews, it is unfortunate that the results of the very detailed blood group studies of its Jewish population undertaken by L. C. and S. P. Dunn and R. Ceppellini are not yet available and that only a preliminary report[41] has yet been published.

In order to test Lundman's analysis of the data, I have plotted as separate points on a gene frequency diagram (see right) the results of all the separate surveys listed by Mourant *et al.*[179] of Jewish populations living in or coming from specified parts of central and eastern Europe, including the European parts of the U.S.S.R. These sets of results are about twice as numerous as those listed by Lundman. They show a central cluster around the gene frequencies A, 28.5 percent, B, 12.5 percent, and a less well defined series with A gene frequencies around 25 percent and a wide range of B. These, simply as a matter of classification, appear broadly to represent Lundman's two series: each is highly heterogeneous in country of residence but the lower A frequencies come, on the whole, from farther west than the higher—a conclusion which might have been reached by considering the national averages used in my original analysis.

The heterogeneity of immediate origin of the group with 28.5 percent of A and 12.5 percent of B genes, and the fact that their A gene frequency is considerably lower than that found in most parts of Asia Minor, suggest that they did not by any means all come in through that territory. There is, however, a further, rather disperse, set of points on the diagram, corresponding to A gene frequencies above 30 percent, and it seems probable that these at least represent populations which have come to Europe from Asia Minor, with its very high A frequencies. This is particularly clear in the case of the Jews of Georgia, with 30.6 percent of A genes, who live very near Asia Minor but among an indigenous population with the lowest A frequencies in eastern Europe.

ABO BLOOD GROUPS OF EUROPEAN JEWS



Three surveys, of Jews from Maramureş, Romania, from Kharkov, Ukraine, and from White Russia, show B gene frequencies above 19 percent. These suggest an origin even farther east than Asia Minor, as do the still higher B frequencies found in the culturally distinct Karaite and Krimchak communities of the Soviet Union.

I should add that, in criticizing Dr. Lundman's conclusions based on blood groups, I am not questioning his historical statements, which are based on a knowledge of Jewish history clearly much more extensive than my own.

The only Jewish community in western Europe for which we have adequate data is that of the Netherlands, with the lowest known B frequency of any Jewish community and with both A and B frequencies almost identical with those of the local non-Jews; there can hardly be any doubt that the Jews here have acquired a large number of non-Jewish genes by intermarriage.

Data for the Sephardic Jews, apart from those tested in Israel, are very scanty. We can be certain that the Jews of the Netherlands, just mentioned, though probably in part of Sephardic descent, differ very widely from their Spanish or Sephardic ancestors. The only known data for Sephardim tested in Europe are those from Yugoslavia, showing 21 percent of A genes and 15 percent of B genes. These figures agree well with the 23 percent of A and 15 percent of B genes of Sephardim tested in Israel. Rather similar figures are found, as we have seen, for the Jewish communities of North Africa. It is to be noted that, although the frequency of B in the Ashkenazim is comparable to that found in most central and eastern European peoples, the frequency in the Sephardim is higher than in any of the autochthonous peoples of western Europe, and that B frequencies are particularly low among Spaniards. Thus it appears likely that the B genes in the Sephardim are derived mainly from their east Mediterranean ancestors.

The diagram for the Jews of Asia (see right) is even more confusing than that for Europe. Both A and B frequencies of the Jews are high, as are the corresponding frequencies of the peoples among whom they live or from whose regions they take their name. But in Asia the Jews appear to have more diversity of frequencies than non-Jews. One is tempted to see in this an effect of inbreeding, each Jewish community tending to develop somewhat extreme gene frequencies as a result of genetic drift. The explanation, however, probably is that non-Jewish communities of southwestern and central Asia differ more widely from one another in blood group frequencies than the currently available data indicate, and that the Jews reflect these differences.

Entirely distinct from other Jewish communities in Asia so far examined are the Yemenite Jews and the Samaritans, both communities having very low frequencies of both A and B, similar to those of the Arabs of Arabia. Of Samaritan blood groups we know nothing beyond the ABO frequencies of a relatively small number, but the Yemenites have been very fully studied and are further discussed below with regard to their Rh and MN blood groups.

The ancient community known as the "Black Jews" of Cochin shows a higher frequency of B than of A. This is true both of those tested in India and of immigrants tested in Israel, though the absolute frequencies found differ considerably. The preponderance of B over A is typical of many Indian populations, though not of most of those of the Cochin region itself. Blood groups may, however, be regarded as supporting skin color in suggesting a considerable measure of indigenous Indian ancestry. The Bene-Israel Jews of Bombay have rather similar A and B frequencies. The "White Jews" of Cochin, on the other hand, have an exceptionally high A frequency, but the community is very small and there are indications that the over-all frequencies are unduly influenced by inbreeding.

The Rh Blood Groups

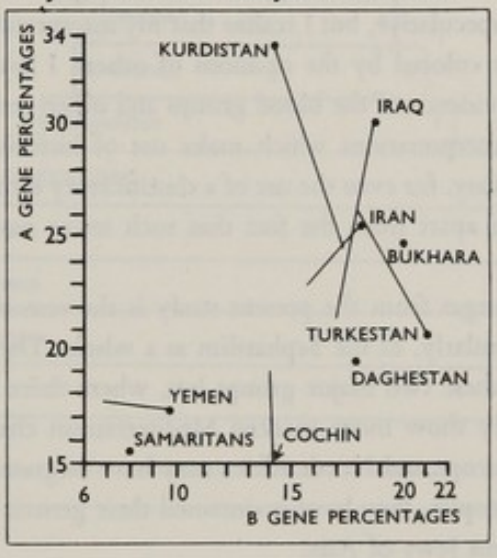
The observations on the Rh blood groups of Jewish communities are fairly numerous but are confined to countries outside Europe, a large proportion having been carried out on recent immigrants to Israel by Dr. Gurevitch and his colleagues.[49, 108-113, 160]

Where Rh tests have been done on Jewish populations a range of sera have in nearly all cases been used, so that it has been possible to calculate the frequencies of most or all of the gene complexes (such as CDe) present in the population.

The observations of Gurevitch *et al.*[111] on Sephardic and Ashkenazic immigrants show that both these important groups of Jews have a blood group constitution which might be accounted for by the mixing of a Mediterranean population with one from central or northern Europe. As might be expected, the Sephardim are nearer to the Mediterranean type, having a higher frequency of CDe and lower frequencies of cDE and cde than the Ashkenazim. In addition, both these populations have a frequency of cDe distinctly higher than is found in the peoples of northern and central Europe or in most Mediterranean peoples; this almost certainly originates in Africa south of the Sahara Desert, where its frequency is from 45 to 90 percent as compared with 2 to 3 percent in Europe. Most Jewish populations have from 5 to 10 percent of this gene combination, whereas Moslem peoples of the Near East have from 10 to 20 percent. In both cases it is almost certain that the excess over 3 percent, if not the whole, came, directly or indirectly, from Africa and hence that the Jews in general, and especially the Sephardim, have several percent of an African component in their ancestry.

Generally speaking, the Jewish populations of North Africa have Rh frequencies in agreement with those of the typical Sephardim but with the Mediterranean features, not surprisingly, more marked and the African cDe component a little higher.

ABO BLOOD GROUPS
IN JEWS AND NON-JEWS OF ASIA



The Jews of Kurdistan, Baghdad, and Persia show, broadly speaking, the same features as those already mentioned for Jews from Europe. They have a high frequency of CDe, but the value of 60 percent reached by the Persian Jews is perhaps a mark of Asiatic as much as of Mediterranean origin. They have a rather high frequency of cDE, which is a feature of populations of the Near East generally as well as of northern and eastern Europe. Frequencies of cDe are variable but sufficiently high to indicate the presence of an African component. The frequency of cde is lower than in the Sephardim and Ashkenazim but not so low as the most extreme figures found in the Mediterranean Basin in non-Jews. The low figures may nevertheless be in part the result of the presence of Asiatic components in the population.

We have already seen that the ABO blood group frequencies of the Yemenite Jews differentiate them from other Jewish populations so far examined and also, on the same basis, that there is little difference between Yemenite Jews and Yemenite Arabs. The Rh groups of both populations fit well into the Mediterranean picture and also seem to support the hypothesis of a common origin for the two populations. The one point which remains doubtful is that of the amount of African admixture present in the Jews and in the Arabs in this region. Much depends upon how we interpret the presence of 20 percent of the combination cD^{u}e in the Yemenite Jews. It is possible that this is a relatively local eastern Mediterranean character. On the other hand, there is a possibility that, for technical reasons which have not yet been fully defined, the entity which is diagnosed in this survey as cD^{u}e may not differ from what is diagnosed in other surveys, including that of the Yemenite Arabs, as cDe, which is certainly mainly of African origin.

Discussion

In describing the blood-group pictures of particular Jewish populations, we have reached certain limited conclusions as to their origins. It is now necessary to see whether and to what extent the data can be made to yield more comprehensive conclusions.

Much has been written on the history of the Jews and their migrations. I have read very little of this literature, some of which is speculative, but I realize that my interpretations of blood-group evidence may nevertheless be unduly colored by the opinions of others. I have tried to show what can be deduced directly from the evidence of the blood groups and other genetic factors and to distinguish as clearly as possible any interpretations which make use of historical records or traditions. The distinction, however, is not easy, for even the use of a classificatory term such as "Sephardim" implies community of origin, quite apart from the fact that such terms may have different meanings to different writers.

The chief fact which emerges from the present study is the remarkable uniformity of the Ashkenazim as a whole and, similarly, of the Sephardim as a whole. There is also a rather surprisingly close resemblance between these two major groups but, where there are systematic differences, the Sephardim not unexpectedly show more marked Mediterranean characters than the Ashkenazim. Thus, though the Jews of Europe and North Africa may have migrated widely and inter-married to some extent with various peoples, they have maintained their genetic identity more obviously than have the more heterogeneous Jews of Asia.

In regard to the latter, no generalizations can be made. Before we can interpret the considerable but heterogeneous body of blood-group data available we need much further information on the blood groups of the autochthonous populations of the southern part of the Soviet Union and of other parts of southwest Asia.

Two Asiatic Jewish populations show features of particular genetic interest: one is the Yemenites, who, as we have seen, are almost identical genetically with the Yemenite Arabs; the other is the Jews of Iraq, the so-called "Babylonian Jews," who claim to have remained a closed population since the exile to Babylon in 586 B.C.E. The remarkable high frequency shown by Szeinberg *et al.*[244] (see also p. 69 and p. 271) for the character of G6PD deficiency in this population gives some genetic support to this claim: For the purpose of comparison it is important that studies of this biochemical character should be made on larger numbers of Jews of various origins and on other populations of the Mediterranean region.

In my opinion we cannot at present, except in a few cases, correlate the varying blood-group frequencies shown by local surveys with the detailed history of the communities concerned, but it would perhaps be possible to do this, at least in part, if the Blood Transfusion Services in Israel were to record the precise birthplace of every donor and the records could be analyzed at a single coordinating center similar to the Nuffield Blood Group Center in Britain. This, however, is a task which must begin at once if it is to be done at all. Although elaborate blood grouping would be of value, it is out of the question on the scale required for such a survey; and, fortunately, it is the ABO groups, determined for every donor, that are of more value than all the others together in an investigation of the kind suggested.

Although the study of the blood groups and other genetic characteristics of the Jews has thus far solved comparatively few problems, it can nevertheless be said that the results obtained are sufficient to show that this approach to problems of Jewish classification and origins is of great value and to make it desirable that the work be continued and extended.

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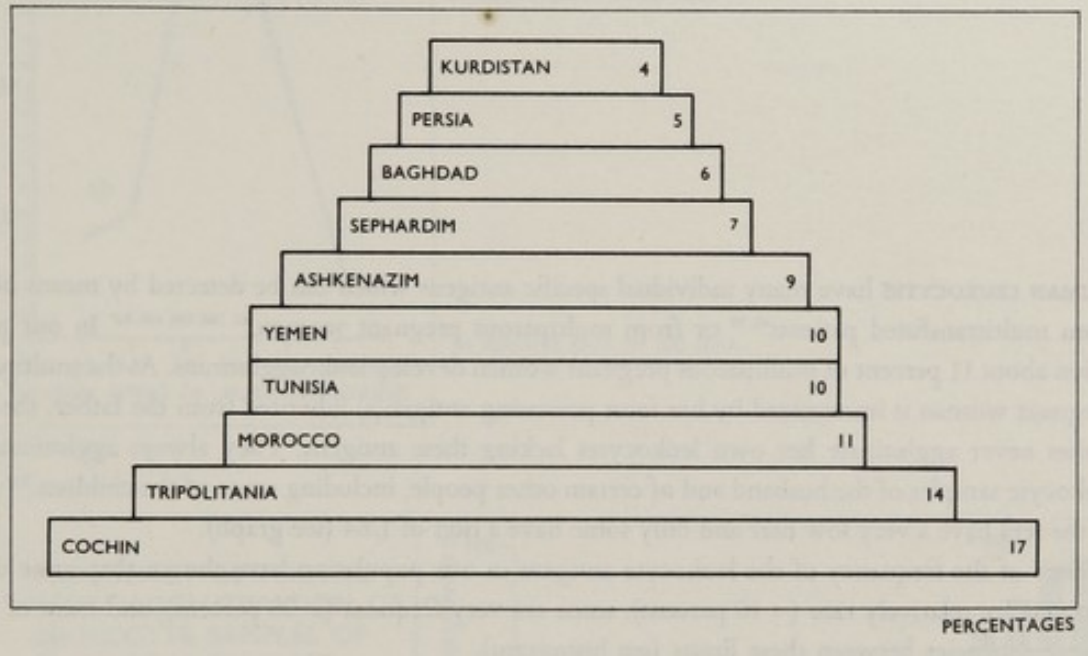
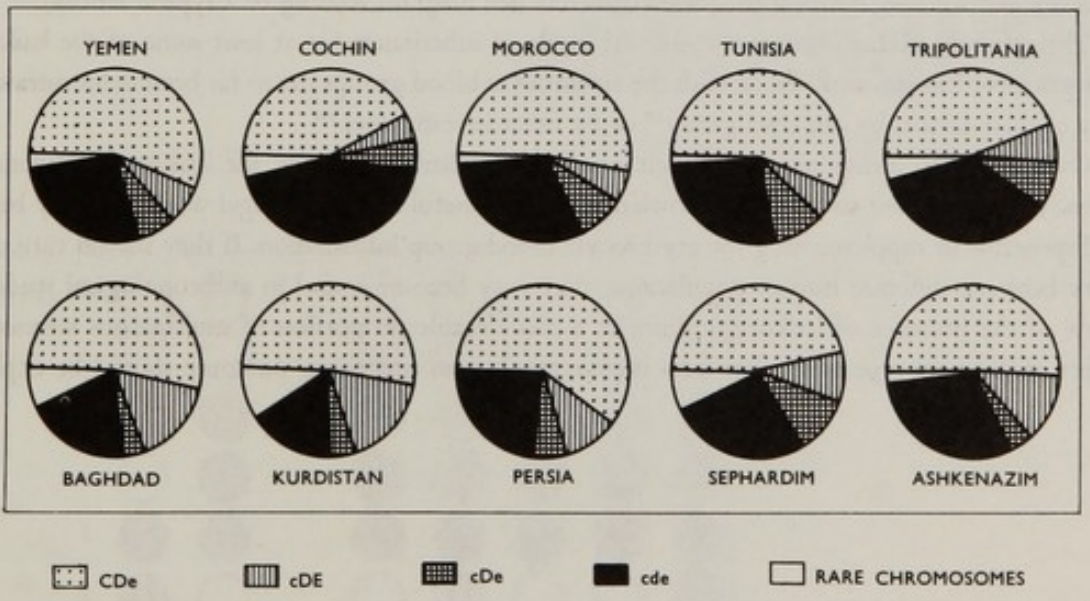
FREQUENCIES OF RHESUS-NEGATIVE INDIVIDUALS
IN VARIOUS COMMUNITIES



FREQUENCIES OF THE RHESUS-CHROMOSOMES
IN VARIOUS COMMUNITIES



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HUMAN LEUKOCYTES have many individual specific antigens which can be detected by means of sera from multitransfused patients[42, 70] or from multiparous pregnant women.[82, 100, 188, 189, 207] In our population about 11 percent of multiparous pregnant women develop leukoagglutinins. As the multiparous pregnant woman is immunized by her fetus possessing antigen(s) inherited from the father, the antibodies never agglutinate her own leukocytes lacking these antigens. They always agglutinate the leukocyte samples of the husband and of certain other people, including some of the children.[207] Most of the sera have a very low titer and only some have a titer of 1/64 (see graph).

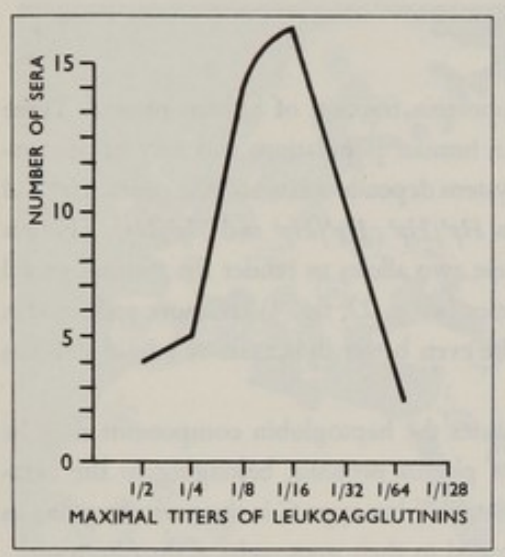
Tests of the frequency of the leukocyte antigens in our population have shown that some of the antigens are relatively rare (< 10 percent), some are very frequent (> 90 percent), and most of them have frequencies between these limits (see histogram).

In cases of monozygotic twins, the leukocyte antigens detectable by means of our sera from multiparous pregnant women have been found to be identical. Similar results have been obtained by other authors[71, 147] employing sera from multitransfused patients.

The great variety of leukocyte antigens present in our population may be gauged from the fact that so far not a single sib pair tested by us was identical in this respect. This implies that all families investigated were segregating for these characters (see diagram relating to a typical family).

These family studies indicate a dominant mode of inheritance for at least some of the leukocyte antigens. No linkage with sex or with the erythrocyte blood groups has so far been demonstrated for any of these factors by our own group[100] or by other investigators.[188]

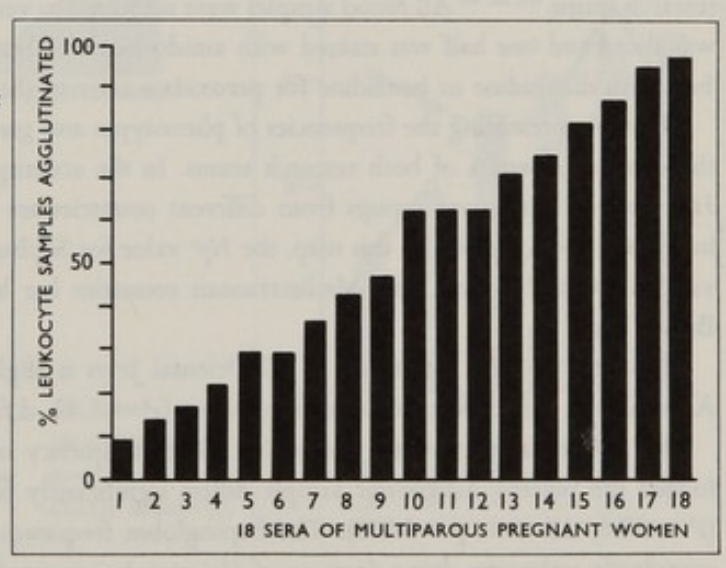
Owing to their individuality and their strictly Mendelian inheritance, the leukocyte antigens may already in the present state of our knowledge be very useful in medico-legal work and may become indispensable in supplementing the erythrocyte blood group information. If they should turn out to vary between different human populations, they may become a tool in anthropological studies. In view of the presence of leukoagglutinins in a considerable proportion of multiparous women, the effect of this new type of mother-fetus incompatibility on pregnancy outcome should be explored.

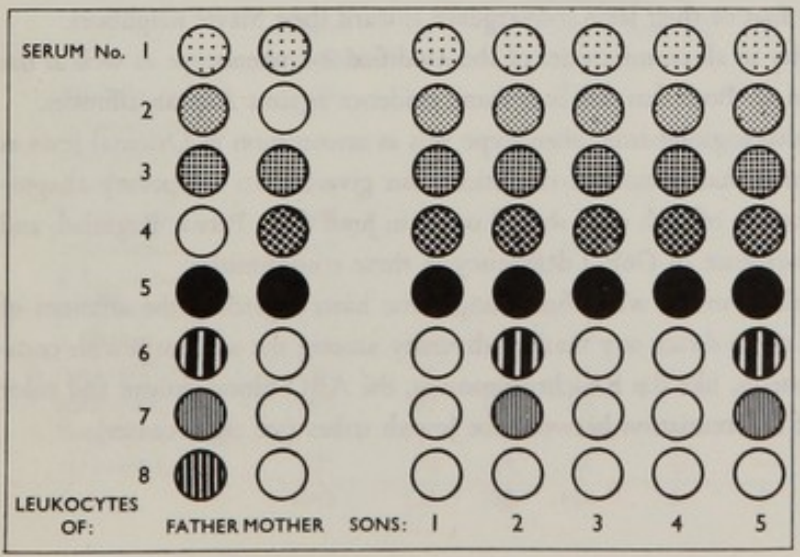


FREQUENCY OF MAXIMAL TITERS OF UNSPECIFIED LEUKOAGGLUTININS FOUND IN SERA OF MULTIPAROUS PREGNANT WOMEN

54 POSITIVE OUT OF 600 SERA

FREQUENCY OF POSITIVE LEUKOAGGLUTINATION OF LEUKOCYTE SAMPLES OF 50 DONORS BY 18 SERA OF MULTIPAROUS PREGNANT WOMEN





ANTIGENIC CONSTITUTION OF THE LEUKOCYTES IN MEMBERS OF ONE FAMILY EXAMINED WITH SERA OF MULTIPAROUS PREGNANT WOMEN

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THE HAPTOGLOBINS are components of the alpha-2 glycoprotein fraction of human plasma. Three different haptoglobin phenotypes coexist quite generally in human populations and may be demonstrated by starch gel electrophoresis.[226] This polymorphic system depends on two allelic genes, Hp^1 and Hp^2, and the three common zygotes have the constitution Hp^1/Hp^1, Hp^1/Hp^2 and Hp^2/Hp^2. There is sufficient ethnic variation in the relative frequencies of these two alleles to render the systems useful in biochemical anthropology.[233] A series of additional alleles (see p. 22, fig. 4) are more restricted in their geographical distribution and, for this reason, may be even better indicators of ethnic affinities than the main alleles.

The same run of starch gel electrophoresis which separates the haptoglobin components may be utilized to demonstrate the transferrins, another group of plasma proteins, belonging to the beta-globulin fraction. The transferrins also exhibit genetic variation[227] but type C is the prevailing one in all populations studied, the other types being rare and limited in their geographical distribution.

The haptoglobins and transferrins of various Israeli groups have been studied by two independent research teams.[101, 202, 203] All blood samples were subjected to vertical starch gel electrophoresis. Each gel was sliced and one half was stained with amido-black or brome-phenol-blue for protein, the other half with dianisidine or benzidine for peroxidase activity (hemoglobin).

The table presenting the frequencies of phenotypes and genes in the Israeli populations is based on the combined results of both research teams. In the accompanying map the concentrations of the Hp^1 gene in immigrant groups from different countries are compared with those of the non-Jews inhabiting these regions. In this map, the Hp^1 value for Sephardic Jews who have been scattered over various south European and Mediterranean countries has been entered, rather arbitrarily, in the Balkan area.

Although the Hp^1 frequency of all Oriental Jews is slightly lower on the whole than that of Ashkenazim, this difference is not significant ($\chi^2 = 1.42$, d.f. $= 1$, $0.3 > p > 0.2$).

The Ashkenazim exhibit a somewhat lower frequency of the Hp^1 gene than west Europeans. Indeed the present Ashkenazic sample differs significantly from a large sample of west Europeans[97] ($\chi^2 = 38.6$, d.f. $= 1$, $p < 0.001$). The haptoglobin frequencies of Slavic peoples are, as yet, almost completely unknown, but a decrease of Hp^1 may be expected as we pass eastward in Europe. It may well remain impossible to decide whether the haptoglobin frequencies of Ashkenazic Jews reflect their early origin from the Near East or their later convergence toward their Slavic neighbors.

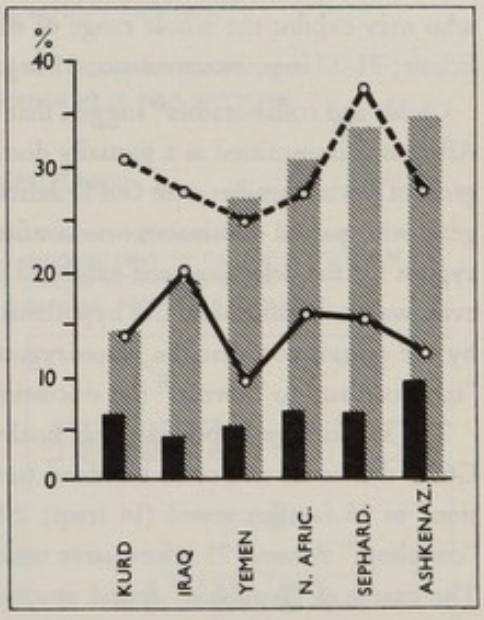
It is of interest to note the rarity in all communities of the modified 2-1 phenotype as well as the absence of transferrins other than C. Both features bear some evidence against African affinities.

Contrary to expectation, the ahaptoglobinemic phenotype was as uncommon in Oriental Jews as in Ashkenazim. Since it is assumed that hemolytic conditions can give rise to temporary ahaptoglobinemia, a considerable proportion of such cases should occur in Jews from Persia, Baghdad, and Kurdistan in view of the high incidence of G6PD deficiency in these communities.

The haptoglobin and transferrin systems, while furnishing some hints regarding the affinities of Jews to other ethnic groups, do not indicate any marked diversity among the various Jewish communities. Other polymorphic systems, like the Rh-chromosomes, the ABO blood groups and color blindness are better indicators of differentiation between the Jewish tribes (see right center).

FREQUENCY OF Hp¹-GENE AMONG GENTILES AND JEWS

SOME POLYMORPHIC SYSTEMS IN THE JEWISH COMMUNITIES



Haptoglobins in Various Communities*

	Number investigated	PHENOTYPES 1-1	1-2	2-2	mod. 2-1	0	Frequency of Hp^1 gene
1. Moslems, Israel	69	6	24	38	—	1	0.265
2. Oriental Jewish communities							
a. North Africa	223	17	90	113	1	2	0.282
b. Near East	48	2	21	25	—	—	0.260
c. Baghdad	197	14	79	103	1	—	0.273
d. Kurdistan	96	5	48	41	—	2	0.308
e. Persia	101	8	43	50	—	—	0.292
f. Yemen	41	2	16	22	—	1	0.250
3. Sephardic Jews	44	5	23	16	—	—	0.375
4. Ashkenazic Jews	669	56	290	320	—	3	0.302
5. Israeli Jews unclassified	175	20	69	86	—	—	0.311
Total	1663	135	703	814	2	9	

* All transferrins were of type C.

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DURING THE PAST five years our group has studied the deficiency of the enzyme G6P dehydrogenase in Israel.[2, 69, 196-97, 200-01, 206, 236-38, 240-45] The problems investigated include the mode of inheritance of this defect, its ethnic distribution, its viability effects, and various aspects of its pleiotropic expression and its physiology.

The family studies and the population surveys were carried out mostly by means of the glutathione stability test of Beutler.[36] Since in many cases the bloods had to be stored overnight before testing, it was found convenient to add 400 mg. percent glucose to the blood before storage in the refrigerator.

The deficiency of the enzyme G6PD interferes with the reduction of TPN and GSSG. Current knowledge on the metabolic pathway which is blocked in enzyme-deficient cells is summarized in the chart, which also emphasizes various controversial points requiring further study. Beutler's method furnishes an indirect estimate of G6PD activity based on the concentration of reduced glutathione in the blood sample after two-hour incubation with phenylhydrazine.

Males were classified as "deficient" if their blood sample contained less than 20 mg. glutathione per 100 ml. red cells after incubation. The value for normal males is usually over 35 mg. percent. Females, who may exhibit the whole range of intermediate values, were classified as follows: 0-20 mg., deficient; 21-30 mg., intermediate; 31 mg. and more, normal.

Childs and collaborators[57] suggest that the G6PD deficiency giving rise to primaquine sensitivity in Africans is transmitted as a partially dominant sex-linked trait. We have collected data on 193 pedigrees of Jewish families with G6PD deficiency. In 152 of these pedigrees the hypothesis of an X-linked gene with partial dominance was confirmed, since females shown by the family data to be heterozygous for the defective gene exhibited intermediate glutathione values. A series of pedigrees, however, was at variance with this hypothesis (see atypical pedigrees, right). They can all be accounted for by the assumption that the heterozygous female may exhibit any value from "deficient" through "intermediate" to "normal" (see discussion of this point in the light of M. Lyon's hypothesis,[158] p. 113).

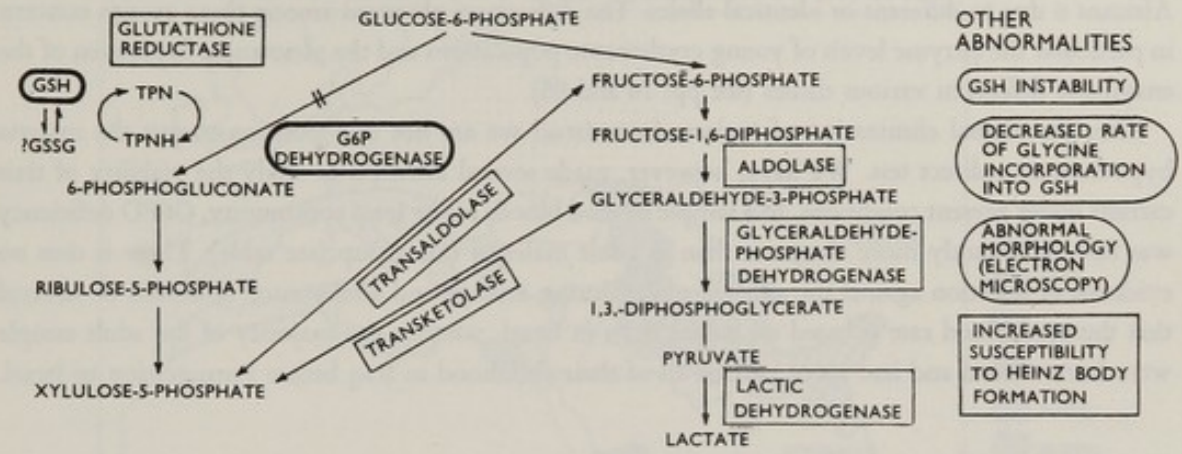
The sex-linkage hypothesis was finally confirmed by collecting data on families segregating for G6PD deficiency and color blindness (see pedigrees, right). The two defective genes were in "repulsion" in 16 families tested (14 Iraqi; 2 Kurdish), and only 3 families (2 Iraqi; 1 Kurdish) showed "coupling." Among 75 informative males investigated not a single case of crossing-over was found. The excess of "repulsion" found among Jews in contrast to the excess of "coupling" in Sardinian populations[223] is fully discussed elsewhere in this volume (see pp. 108 and 111).

Our estimate of the concentration of G6PD deficiency among the communities of Israel was based on unrelated males chosen at random. About half of the individuals were hospital patients or donors of the Tel-Hashomer blood bank. This "hospital sample" does not include persons whose blood was sent to the laboratory because of suspected hemolytic disease or enzyme deficiency, and relatives of such people were also excluded.

The other half of the sample was collected in settlements of known ethnic composition or at the airport from new immigrant groups. Relatives closer than first cousin were excluded from the calculation. As a rule the father and the oldest son of each family were included, since their X-chromosomes are of independent origin.

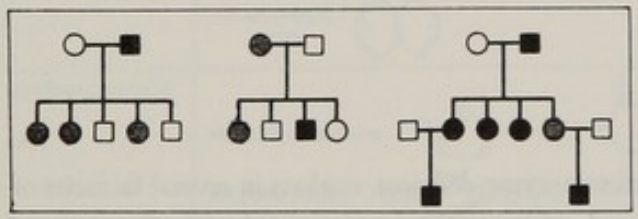
The distribution of this trait among the various Jewish communities is represented on the map. The extreme diversification of the Jewish tribes which is indicated by this character and not borne out by other anthropological features has been discussed elsewhere in this volume (pp. 69 and 100). Obviously no final interpretation of this geographical distribution can be offered before the completion of the corresponding map indicating the concentration of G6PD deficiency in the non-Jewish populations around the Mediterranean Basin and in the Middle East.

ABNORMAL PARAMETERS OF G6PD DEFICIENT RED BLOOD CELLS



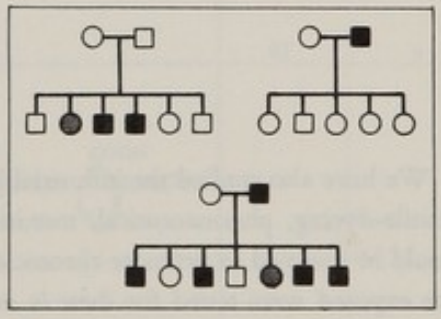
INHERITANCE OF G6PD DEFICIENCY

TYPICAL PEDIGREES CONSISTENT WITH THE HYPOTHESIS OF AN INCOMPLETELY DOMINANT GENE LOCATED ON THE X-CHROMOSOME

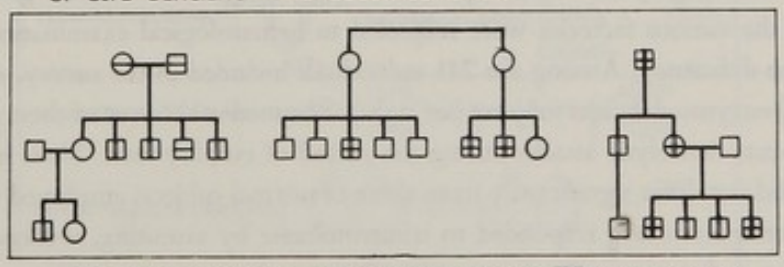


NORMAL
INTERMEDIATE EXPRESSION OF G6PD DEFICIENCY
FULL EXPRESSION OF G6PD DEFICIENCY

ATYPICAL PEDIGREES INCONSISTENT WITH THE HYPOTHESIS, UNLESS NON-PENETRANCE IN SOME FEMALES IS ASSUMED



REPRESENTATIVE PEDIGREES DEMONSTRATING LINKAGE OF G6PD DEFICIENCY AND COLOR BLINDNESS



G6PD DEFICIENCY DEUTERANOMALY DEUTERANOPIA

DISTRIBUTION OF G6PD DEFICIENCY AND COLOR BLINDNESS IN COMMUNITIES OF IRAQ & KURDISTAN

	% G6PD DEFICIENCY	% COLOR-BLINDESS
IRAQ	24.8	3.8
KURDISTAN	58.2	4.9

% G6PD DEFICIENCY AMONG COLOR-BLIND IRAQI MALES: 12.3

It is impossible at the present stage to decide whether G6PD deficiency in Jews, Sardinians, and Africans is due to different or identical alleles. The differences observed among these groups concern in particular the enzyme levels of young erythrocyte populations and the pleiotropic expression of the enzymatic defects in various tissues (see pp. 76 and 85).

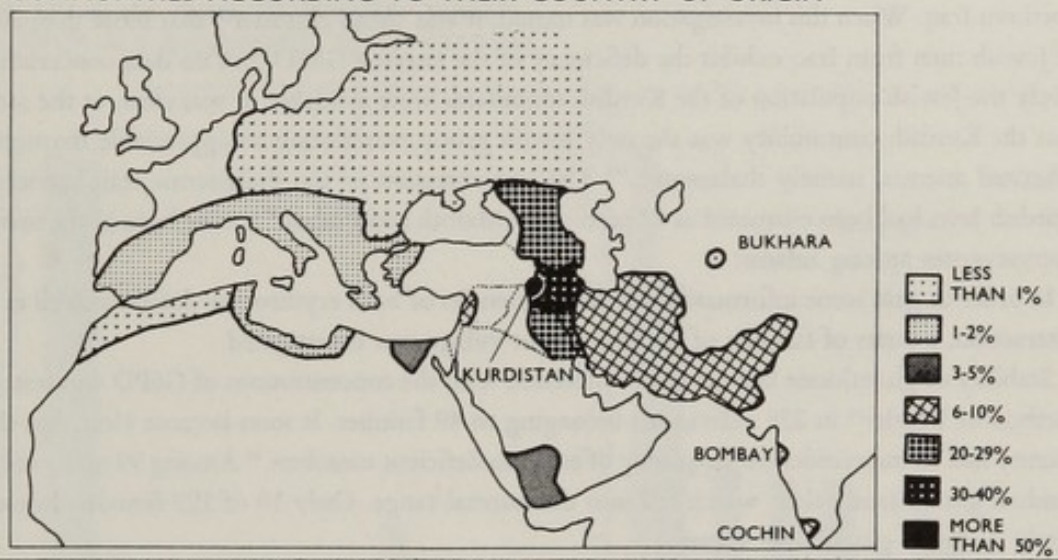
After the virtual elimination of malaria from Israel we are not in a position to put the malaria hypothesis to a direct test. We have, however, made several attempts to study the viability of trait carriers under present conditions. In a sample of cord bloods of the Iraqi community, G6PD deficiency was not significantly more common than in adult males of this group (see table). There is thus no evidence of selection against the affected males during infancy and adolescence. It should be stressed that the cord blood rate is based on babies born in Israel, whereas the majority of the adult sample were born abroad and had spent part or all of their childhood in Iraq before immigration to Israel.

FREQUENCY OF G6PD DEFICIENCY AMONG MALES OF THE JEWISH COMMUNITY FROM BAGHDAD

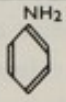
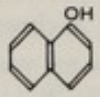
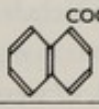
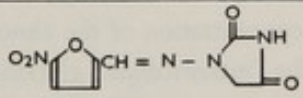
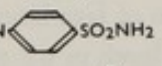
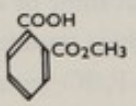
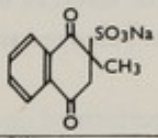
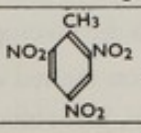
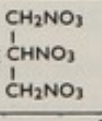
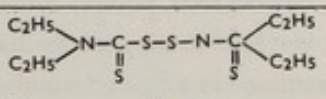
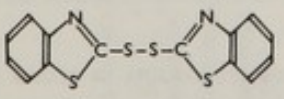
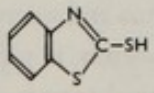
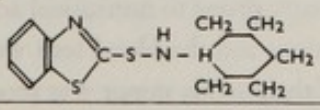
Age group	*Number examined*	*Number deficient*	*Percent deficient*
Cord blood and newborn	71	19	26.8
Above 15 years	850	211	24.8
	$\chi^2 \sim .14$	$p > 0.75$	

We have also studied the industrial hazard to enzyme-deficient workers in several factories of the textile-dyeing, pharmaceutical, munitions, and rubber-tire industries, employing chemicals which could be assumed to promote chronic or acute hemolysis. Various compounds to which the workers are exposed were tested for their *in vitro* influence on glutathione stability by incubating enzyme-deficient erythrocytes with various concentrations of these compounds instead of acetyl-phenyl-hydrazine. The table (right) lists the compounds which were found to affect glutathione stability. The workers of the various factories were subjected to hematological examinations and were also tested for enzyme deficiency. Among the 241 individuals included in the survey, there were 25 (or about 10 percent) enzyme-deficient subjects (see right). The medical history of these persons contained no evidence of acute hemolytic attacks during the period of employment. Their hemoglobin levels and hematocrit did not differ significantly from those of normal subjects employed in the same plant. A single trait carrier from Iraq responded to trinitrotoluene by vomiting, weakness, and increased reticulocyte counts and coproporphyrin excretion. There is, however, no evidence that this response was due to the enzyme deficiency. Industrial contact with the various substances listed by us was thus well tolerated by 24 out of 25 enzyme-deficient subjects included in this survey.

DISTRIBUTION OF G6PD DEFICIENCY AMONG JEWISH COMMUNITIES ACCORDING TO THEIR COUNTRY OF ORIGIN



HEMOLYTIC HAZARD TO ENZYME-DEFICIENT INDUSTRIAL WORKERS

TYPE OF FACTORY	PROCESSED COMPOUNDS AFFECTING GLUTATHIONE (GSH) STABILITY.	NUMBER WORKERS EXAMINED	NUMBER ENZYME DEFICIENT
TEXTILE DYEING PLANTS	ANILINE  β-NAPHTOL & DERIVATIVES  β-NAPHTOLIC ACID 	87	9
PHARMACEUTICAL	NITROFURANTOIN  SULFONAMIDES  ACETYLSALICYLIC ACID  VITAMIN K ANALOGUES 	61	2
MUNITION	TRINITROTOLUENE  NITROGLYCERINE  $KClO_3$	46	11
RUBBER-TIRE FACTORY	TETRAETHYL THIURAM DISULFIDE  BENZOTHIAZYL DISULFIDE  MERCAPTOBENZOTHIAZOLE  N-CYCLOHEXYL-2-BENZO-THIAZOLE SULFONAMIDE 	47	3
	TOTALS	241	25
	HEMOLYTIC ATTACKS	—	—

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THE DATA REPORTED here were collected during 1958 and 1959 in the Jerusalem corridor in an immigrant village settled by Jews who had arrived in 1951 from four hamlets in the Kurdish mountains of northern Iraq. When this investigation was started, it was already known[244] that more than 20 percent of Jewish men from Iraq exhibit the deficiency of the enzyme G6PD, but no data concerning exclusively the Jewish population of the Kurdish mountains were available. It was clear, at the same time, that the Kurdish community was the only Jewish group manifesting an appreciable frequency of an inherited anemia, namely thalassemia.[164] The concentration of the thalassemia trait carriers among Kurdish Jews had been estimated at 12 percent by Matoth and Pinhas[163] on the basis of the incidence of homozygotes among infants.

In order to gain some information on the frequencies of both erythrocyte defects as well as on their interaction, a series of families of the immigrant village was investigated.

Stability of glutathione known to be correlated with the concentrations of G6PD was tested by the method of Beutler[36] in 228 individuals belonging to 49 families. It soon became clear that this community had an unprecedented frequency of enzyme-deficient members.[64] Among 99 males only 12 had residual glutathione values which fell into the normal range. Only 10 of 129 females showed "definitely normal" glutathione values.

The frequency of the abnormal gene was estimated on the assumption of complete X-linkage. In view of the wide phenotypic range of the heterozygous females the gene count was based on males, excluding relatives closer than first cousins. As a rule, the father and the oldest son investigated were included in the count, since their X-chromosomes are of independent origin.

A number of boys mostly below ten years of age exhibited GSH values between 30 and 55. Because of the difficulty of classifying such individuals they were not included in the gene count and the next male in the pedigree with a clear-cut value (residual glutathione in mg./100 ml. RBC: 0-29, deficient; 55-80, "normal") was chosen. Among 53 males thus counted, 47 were enzyme deficient, leading to an estimate of 88.7 ± 4.3 percent for the concentration of the abnormal gene.

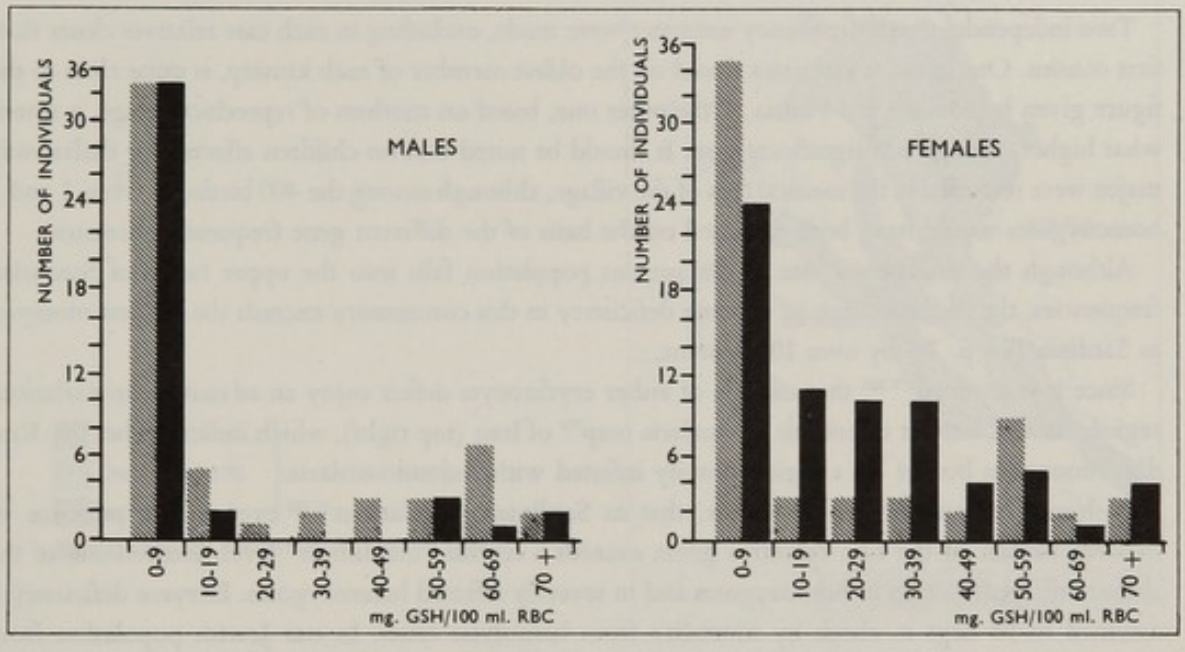
It was suspected that some or all of the "intermediate" glutathione values in young boys might be due to chronic hemolysis resulting from ingestion of fava beans. This hemolysis should increase the proportion of young RBC with higher enzyme levels in the total of RBC population. Indeed, the bloods with intermediate glutathione stabilities belonged mostly to the sample collected during the fava bean season (see bottom right).

A screening test for thalassemia minor was performed on 255 members of 54 families in the settlement. Of these individuals, 225 were also included in the investigation of enzyme deficiency.

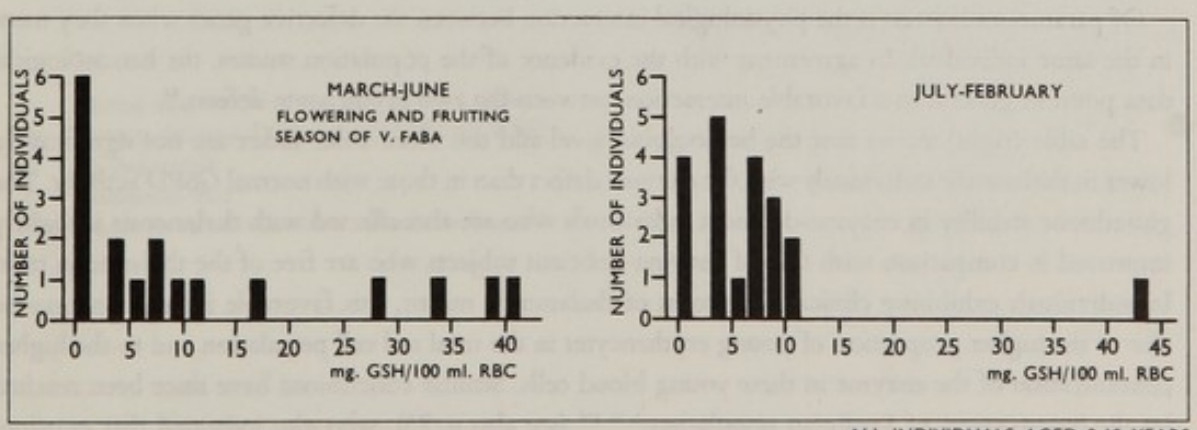
The diagnosis of hypochromic anemia was based on the red cell count and on the Hb level. The presence of microcytosis, ovalocytosis, poikilo-cytosis, basophilic stippling, and target cells in several blood smears of a subject was held to support the diagnosis of thalassemia minor. Hypotonic fragility and alkaline resistance, examined in a limited number of bloods, were not found helpful in detecting mild forms of thalassemia minor.

Hypochromic polycytemia (red cell counts in excess of 5 millions per cu. mm.) was considered typical of thalassemia. However, hypochromia and microcytosis, if not supported by other evidence, were not accepted as reliable criteria of thalassemia, in particular in young children and in multiparous women, who are especially prone to nutritional anemia. All cases suspected of iron deficiency anemia received Imferon injections and the blood tests were repeated not earlier than five weeks after treatment. The diagnosis of thalassemia minor was accepted when the hypochromic anemia and the morphologic changes were not appreciably improved following treatment. Doubtful cases were not

DISTRIBUTION OF G6PD DEFICIENCY AMONG
228 INDIVIDUALS BELONGING TO 49 FAMILIES



DISTRIBUTION OF GSH VALUES AMONG
SENSITIVE MALES AT DIFFERENT SEASONS



ALL INDIVIDUALS AGED 0-10 YEARS

NOTE: MODERATE QUANTITIES OF VICIA FABA GROWN AND CONSUMED IN VILLAGE

(Continued)

included. Observations on increased fractions of fetal hemoglobin and of the A^2 component in thalassemia minor in Kurdish Jews exist,[169] but a complete electrophoretic survey of this population remains to be done.

Two independent gene-frequency estimates were made, excluding in each case relatives closer than first cousins. One of these estimates, based on the oldest member of each kinship, is quite close to the figure given by Matoth and Pinhas;[163] the other one, based on mothers of reproductive age, is somewhat higher, though not significantly so. It should be noted that no children affected by thalassemia major were recorded in the medical files of the village, although among the 400 births between 1 and 3 homozygotes would have been expected on the basis of the different gene frequency estimates.

Although the thalassemia rate in the present population falls into the upper range of Sardinian frequencies, the concentration of enzyme deficiency in this community exceeds the highest observed in Sardinia (see p. 74) by over 100 percent.

Since it is assumed[177, 222] that carriers of either erythrocyte defect enjoy an advantage in malarious regions, it is of interest to consult the malaria map[221] of Iraq (top right), which indicates that the Kurdish mountains border on a region heavily infested with endemic malaria.

It should be remembered, however, that in Sardinian populations[34, 222] even in the presence of malaria, neither of the two defective genes exceeds a certain "maximum" level. Elimination of the thalassemia gene occurs in homozygotes and in severely affected heterozygotes. Enzyme deficiency is assumed to be kept in check by mortality from hemolytic crises. In our Jewish population from northern Iraq, selection against this trait appears to have been ineffective. The "mutant" gene has spread until the normal individuals constitute a minority in the group. The geneticist tends to resort to "drift"—chance fluctuations in small populations—in order to account for such aberrant gene frequencies. The accepted estimate of over 15,000 individuals constituting this population in recent years does not support the hypothesis of drift. Although it is not impossible that this population may have suffered a temporary reduction to much smaller numbers some generations ago, selection against the defective gene should have been at work during population expansion and ever since.

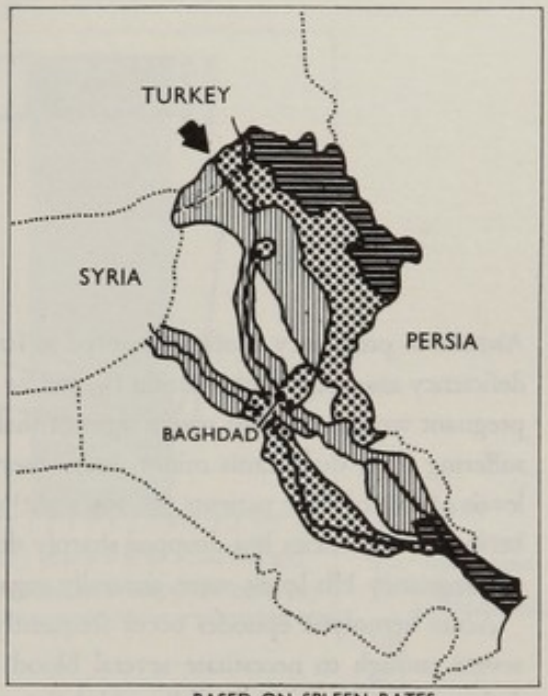
Under present conditions in Israel, we have found very little evidence of such selection against the enzyme-deficient subjects. During eight years of medical supervision there were only four (3 boys, 1 girl) hemolytic incidents ("favism") among 660 children of this population, and not a single death from hemolysis is on record. However, the situation may have been entirely different in Kurdistan in the past.

Of paramount interest is the physiological interaction between the defective genes when they meet in the same individual. In agreement with the evidence of the population studies, the hematological data point in general to a favorable interaction between the two erythrocyte defects.[64]

The table (right) shows that the hemoglobin level and the mean color index are not significantly lower in thalassemic individuals with the enzyme defect than in those with normal G6PD activity. The glutathione stability in enzyme-deficient individuals who are also affected with thalassemia is slightly improved in comparison with that of enzyme-deficient subjects who are free of the thalassemia trait. In individuals exhibiting clinical symptoms of thalassemia minor, this favorable interaction may be due to the higher proportion of young erythrocytes in the total red cell population and to the higher concentration of the enzyme in these young blood cells. Similar conclusions have since been reached by the investigators of Sardinian populations[5, 34, 222] (see also p. 73), who also indicated that enzyme-deficient thalassemic individuals are less liable to clinical favism than other enzyme-deficient subjects.•

• This work was supported by a grant from the Ford Foundation.

MALARIA MAP OF IRAQ



HIGH
INTERMEDIATE } SPLEEN RATES
LOW
ORIGIN OF INVESTIGATED POPULATION

BASED ON SPLEEN RATES, ACCORDING TO SIMMONS *ET AL.* [221]

HEMATOLOGICAL DATA CONCERNING INDIVIDUALS AFFECTED WITH THALASSEMIA AND/OR ENZYME DEFICIENCY

Phenotype		*Hemoglobin*	*Color index*	*GSH*
Anemia	*Enzyme*	*gm. %*		*mg./100 ml. RBC*
t	e	13.13 ± 0.25 (23)	0.96 ± 0.017 (23)	66.04 ± 0.93 (23)
T	e	12.05 ± 0.38 (8)	0.89 ± 0.04 (8)	68.25 ± 2.76 (8)
t	E	12.90 ± 0.12 (125)	0.97 ± 0.007 (125)	5.3 ± 0.42 (125)
T	E	11.60 ± 0.28 (34)	0.81 ± 0.02 (31)	7.1 ± 0.75 (36)

e: normal enzyme (56+ mg. GSH/100 ml. RBC)
E: enzyme deficient (0-20 mg. GSH/100 ml. RBC)
t: no thalassemia
T: thalassemia trait
Numbers in parentheses: number of individuals tested.

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ANEMIA in pregnancy is often observed in Israel.[107, 131, 169, 194, 195, 209] Most cases are characterized by iron deficiency associated with vitamin B_{12} and/or folic acid deficiency. A small but well-defined group of pregnant women exhibits severe signs of thalassemia minor. During the past eight years, 60 women suffering from thalassemia minor were observed during one or more pregnancies. The hemoglobin levels of five of these patients (see top right) ranged from 5.5 to 12.5 gm. percent during the interval between pregnancies but dropped sharply during gestation. Within 2 to 4 weeks after delivery the prepregnancy Hb levels were generally regained.

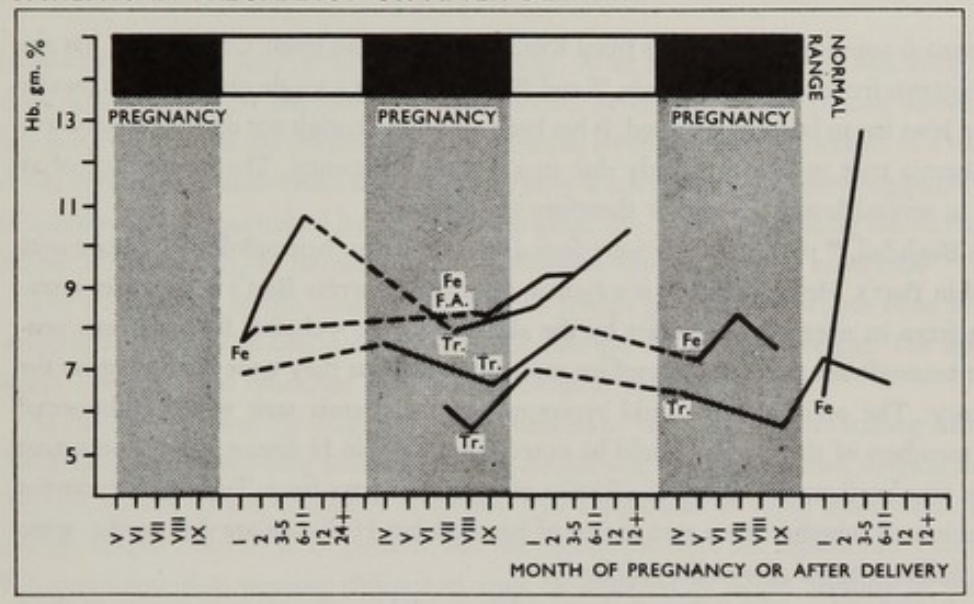
Acute hemolytic episodes occur frequently in thalassemic women during pregnancy and may be severe enough to necessitate several blood transfusions. Marked iron deficiency and vitamin B_{12} deficiency with or without folic acid deficiency are common.

The iron metabolism in four of these patients was studied by intravenous injection of ^{59}Fe. The plasma iron turnover in these pregnant women was low compared with the high turnover rates found in thalassemia patients in general. Thus, thalassemic women in pregnancy may suffer from an iron deficiency similar to that found in other anemic pregnant women.

Chanarin's load test[54, 56] was used to detect pteroylglutamic deficiency in four of these patients (see center) and, contrary to expectation, the clearance rate of the injected pteroylglutamic acid was within the normal range. On the other hand, the bioassay of total folic acid (including the conjugated form of pteroylglutamic acid and the citrovorum factor) indicated that the folic acid content in the serum of thalassemic women can be far below the normal range. This depletion in folic acid may be due in part to hemolysis but is probably largely accounted for by the concentration of this vitamin in the growing fetus.[54, 55]

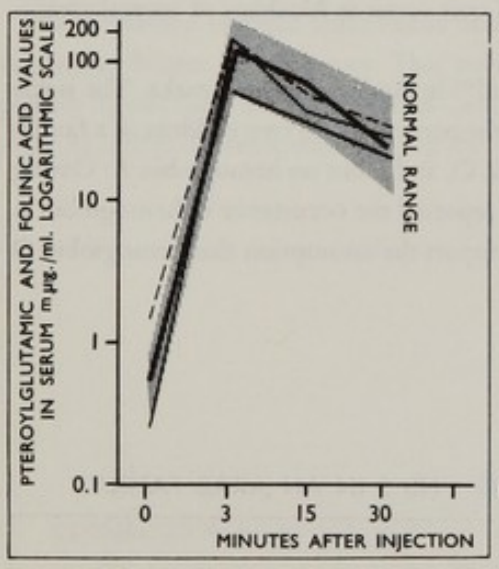
The concentration of vitamin B_{12} was determined in the serum of 10 thalassemic women (see diagram). With few exceptions these patients showed low levels of the vitamin which were similar to those of anemic pregnant women without thalassemia. It is of interest that in two cases of acute hemolytic crisis the level of vitamin B_{12} was very high.

VARIATION OF HEMOGLOBIN LEVELS IN FIVE THALASSEMIC PATIENTS IN PREGNANCY OR AFTER DELIVERY



TREATMENT
Fe ORAL IRON
F.A. FOLIC ACID
Tr. BLOOD TRANSFUSION

CLEARANCE OF INTRAVENOUSLY INJECTED PTEROYLGLUTAMIC ACID IN THALASSEMIC PREGNANT WOMEN

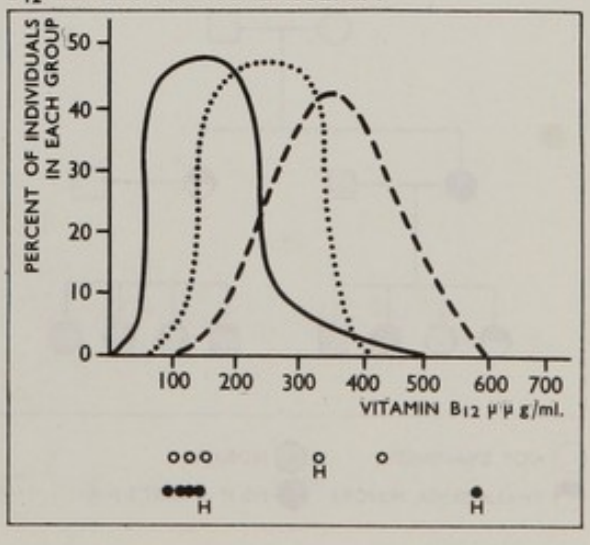


LOAD OF 1 mg.

B_{12} LEVELS IN THALASSEMIA

THE GRAPHS INDICATE THE DISTRIBUTION OF B_{12} LEVELS IN THREE GROUPS OF WOMEN:
- NORMAL NONPREGNANT
- NORMAL PREGNANT
- ANEMIC PREGNANT

EACH DOT INDICATES THE B_{12} LEVEL OF ONE THALASSEMIC WOMAN
- o NONPREGNANT
- ● PREGNANT
- H SAMPLE TAKEN DURING HEMOLYTIC CRISIS



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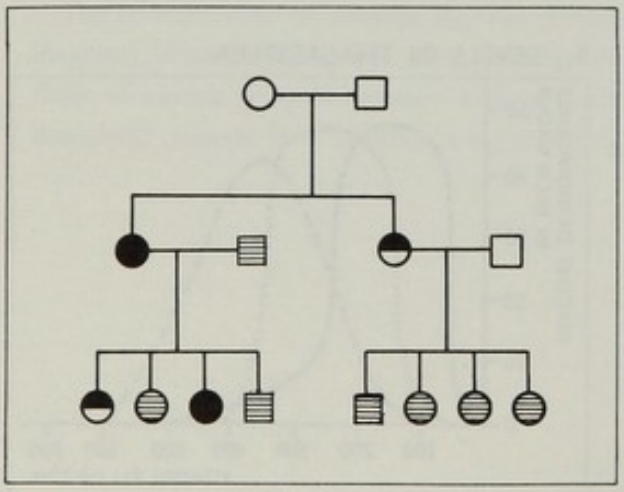
ALTHOUGH thalassemia is common among Jews from Kurdistan[64, 163, 169] and from Urfa[77, 78] and has also been found in immigrants from Bukhara,[213] Syria,[162] and Baghdad,[178] not a single case of a true mutant hemoglobin among Jews has so far been reported. It has been assumed, though not directly demonstrated, that the thalassemia trait in Jews is mostly due to a β-chain deficiency. The occurrence of an α-chain deficiency in several Jewish families is therefore of interest.

In a family from Baghdad,[199] two members were found to suffer from hemoglobin H disease *with* persistent hemoglobin Bart's. Hemoglobin H is a β-chain tetramer, whereas Bart's is a γ-chain tetramer, each differing from its normal counterpart by the absence of two α-chains. Both patients possessed normal adult hemoglobin A and it is therefore most probable that they were heterozygous for the α-chain deficiency. The occurrence of mild symptoms of thalassemia trait without abnormal tetramers in other members of this family should be noted. Hemoglobin H disease *without* persistent Bart's was found in two brothers belonging to a family of Sephardic Jews from Turkey.[142] It cannot be decided at the moment whether these two forms of hemoglobin H disease are due to the same mutant gene or to different types of α-chain deficiency.

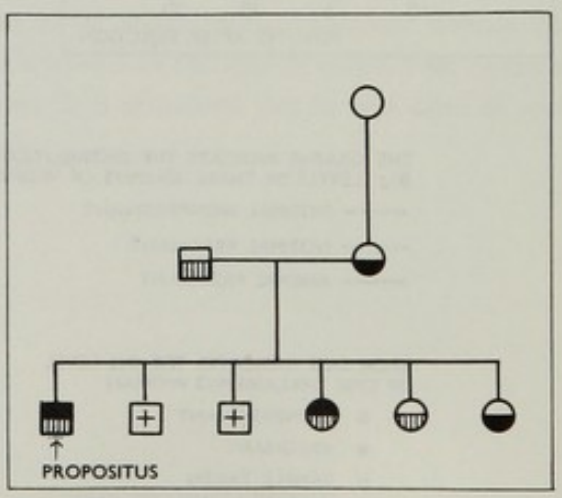
Some of the Israeli Arab tribes possess "true" abnormal hemoglobins, the most common of these being hemoglobin S. Both sickle cell anemia and sickle cell trait occur in Moslems of several areas—*e.g.*, in Wadi Hamman, near Lake Galilee.[176]

Several cases of sickle cell hemoglobin O trait were found[198] in Arabs of Gaser Azarka. The sickle cell trait and the hemoglobin O trait occurred separately in the parents and in two children of a family (see pedigree). Two other children possessed hemoglobins S, O, and F but no hemoglobin A. Owing to a technical error, our earlier publication on this family[198] reported the occurrence of hemoglobin A in these two subjects. However, the present findings fully support the assumption that hemoglobin O is a β-chain mutant.

Hb H DISEASE WITH PERSISTENT Hb BART'S IN A JEWISH FAMILY FROM IRAQ



Hb O + Hb S IN AN ARAB FAMILY



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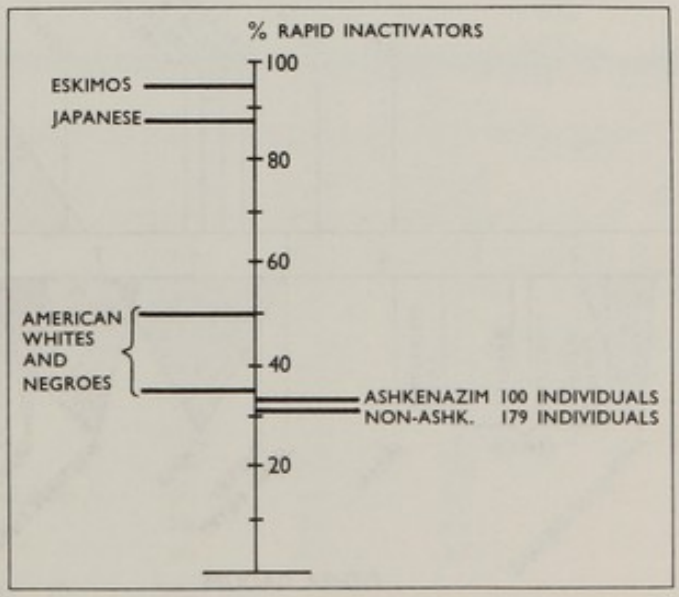
ISONIAZID is widely used in tuberculosis therapy. After administration of this drug its plasma level is determined mainly by the rate of its inactivation. Several investigators have demonstrated in population surveys a bimodal distribution of the plasma levels after administration of a loading dose of this drug, dividing the individuals into rapid and slow inactivators. It has been suggested[143, 193] that the rate of inactivation is determined by an autosomal gene, the "slow" type being the recessive homozygote. Ethnic differences in the frequencies of the recessive types have been observed.[21, 121, 138, 193]

The distribution of this trait among various Jewish groups in Israel has been investigated.[239] The subjects were given an oral dose of 4 mg. isoniazid per kg. of body weight. The level of biologically active isoniazid was estimated by a microbiological method.[29]

As can be seen from the diagram, the frequencies of rapid inactivators among Ashkenazic and non-Ashkenazic Jews were very similar. The non-Ashkenazic group comprised subjects from Iraq, Turkey, Yemen, North Africa, and other countries. The frequencies of rapid inactivators among these subgroups ranged from 25 to 37 percent, but the differences were not significant. This does not preclude the possibility that genuine differences may be detected in larger samples in the future, and the frequency of only 25 percent found in 60 Jews from Baghdad may be suggestive.

The frequency of rapid inactivators observed among Jews is seen to be closely similar to that of American Whites and Negroes. This polymorphic trait which varies sharply between Mongolian peoples on one hand and Africans and Caucasians on the other has not proved so far to be a good indicator of ethnic differentiation among the latter group.

ISONIAZID INACTIVATION



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H. Kalmus A. Amir O. Levine E. Barak E. Goldschmidt A. Adam

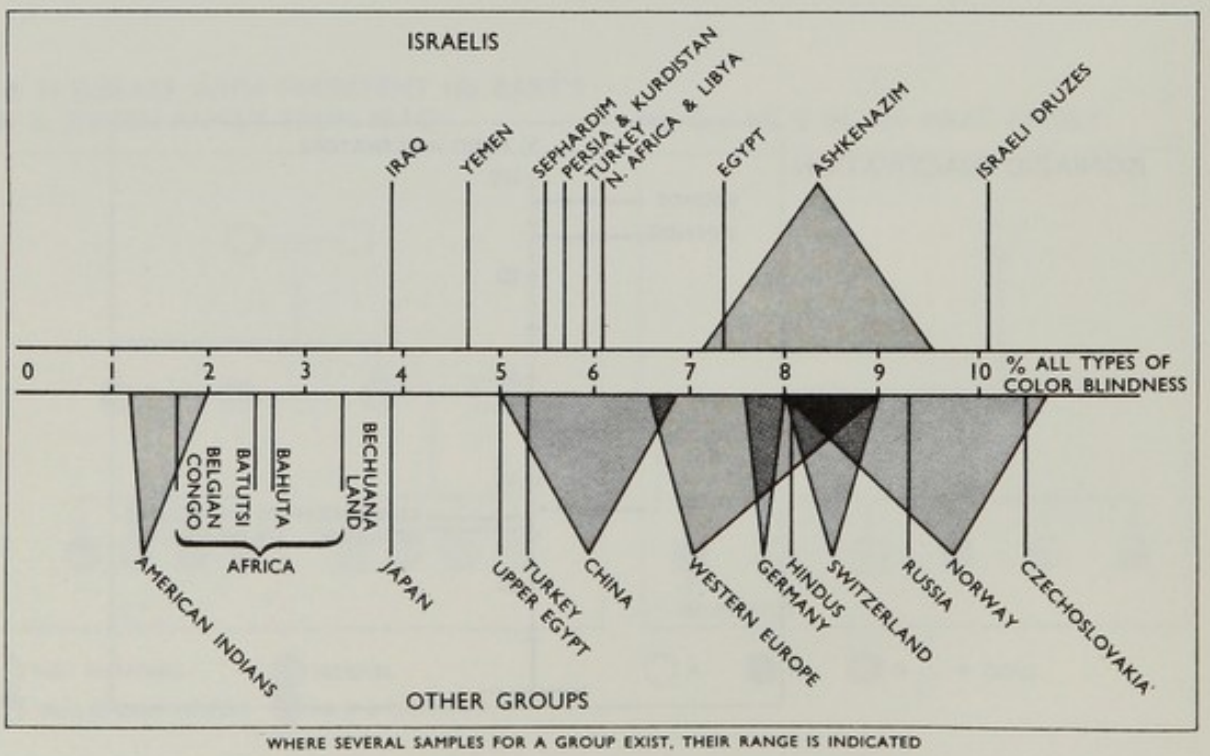
THE INCIDENCE of the various types of sex-linked color blindness in the communities of Israel has been studied over the past few years by two groups of investigators (at the Hebrew University and at Tel-Hashomer) using the Ishihara tables, and data on 7061 male Israelis have been collected. The results of the two teams differed consistently, the Hebrew University group[136] reporting somewhat higher frequencies of color blindness for most communities than the Tel-Hashomer group.[3] However, since the differences between the two subsamples were nonsignificant for each community, the results were pooled and are here presented jointly.

The diagram (see below) shows the over-all frequencies of color blindness for the several Israeli communities and for some other ethnic groups.[90] It can be seen at a glance that this character varies considerably among the Jewish communities, being most common in Ashkenazim and rarest in the Iraqi and Yemenite groups. The Ashkenazic Jews resemble non-Jewish Europeans in this respect, whereas for most of the Oriental Jewish communities no corresponding data concerning non-Jews from the same countries are available as yet. The high "European" frequency of color blindness in the Israeli Druzes is interesting, because this community is believed to have absorbed some of the Crusaders settling in Palestine.

The differentiation between the Jewish tribes with regard to this polymorphic trait may be due to selection, admixture, or their combined effect. The adaptive significance of perfect color vision in males has apparently never been studied.

A more accurate classification of the various types of color blindness based on anomaloscope tests will probably reveal further differences between the Jewish communities. The deutan/protan ratios listed in the table (right) are suggestive, and the Yemenite Jews in particular stand out against the rest. *

RATES OF COLOR BLINDNESS IN COMMUNITIES OF ISRAEL
COMPARED WITH OTHER GROUPS



WHERE SEVERAL SAMPLES FOR A GROUP EXIST, THEIR RANGE IS INDICATED

* This work was supported by a grant from the Ford Foundation.

I. Ashkenazi Ch. Sheba A. Szeinberg

TASTE SENSITIVITY to phenylthiourea is due to a dominant gene, the nontasters being the recessive homozygotes. Human populations are generally polymorphic for this character, and it exhibits geographic variation.

The results of a survey[218] employing the method of Harris and Kalmus[120] in various Jewish groups in Israel are summarized in the table (below). The frequency of nontasters did not differ significantly among subjects from North Africa, Kurdistan, Persia, Iraq and Yemen, Sephardim from the Balkan countries, and Ashkenazim from eastern and central Europe. On the other hand, significantly higher frequencies were observed among the Jews from Cochin and from the island of Gerba (Cochin *vs.* all countries: $p < 0.05$; Gerba *vs.* all countries: $p < 0.01$).

The Cochin Jews resemble in this respect a sample of Indians from Bombay. The Jews from Gerba constitute a small isolate and, in the absence of other explanations, the high frequency of nontasters found among them may be attributable to drift.

The main point of interest emerging from this study is the low rate of the nontaster phenotype in the Jewish communities, including the Ashkenazic group. There are fewer nontasters among Jews than among most Europeans sampled (see p. 24).*

FREQUENCY OF NONTASTERS

Community	*Total no. of subjects*	*% of nontasters* ± ST.E.
Kurdistan	129	13.0 ± 3.0
North Africa	340	15.0 ± 1.9
Iraq and Persia	336	16.0 ± 2.0
Yemen	261	18.0 ± 2.4
Ashkenazim	440	20.7 ± 1.9
Sephardim	101	21.7 ± 4.1
Cochin†	41	31.7 ± 7.2
Gerba†	41	41.4 ± 7.7

* This investigation has been aided by a grant from the Rockefeller Foundation (RF 606101).
† The samples from Cochin and Gerba were small owing to the high consanguinity rates and the exclusion of close relatives from the survey.

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FREQUENCIES OF COLOR BLINDNESS AND DEUTAN/PROTAN RATIOS IN COMMUNITIES OF ISRAEL

Community	*No. males investigated*	*% color-blind*	*Ratio Deutan/Protan*
Ashkenazim	1604	8.0	2.7
Sephardim	253	5.5	1.5
Turkey	272	5.9	3.7
Egypt	162	7.4	2.3
North Africa	618	6.2	2.1
Kurdistan	508	5.7	2.1
Iraq	2142	3.9	3.1
Persia	352	5.7	2.2
Yemen and Aden	511	4.7	1.1
Other Jews	302	5.0	2.0
Druzes	337	10.1	3.7
Total	7061		

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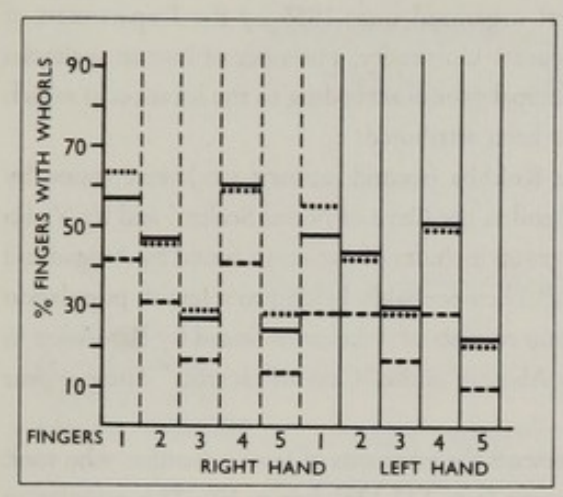
THE WHORLS, loops, and arches of the fingerprint patterns are assumed to be polygenically inherited.[67, 68, 127, 205] Since they have probably only little adaptive significance, they may be particularly useful in anthropological studies.

The fingerprint patterns were studied in eight Jewish populations (from Germany, Poland, Bulgaria, Turkey, Egypt, Morocco, Iraq, and Yemen) and in an unselected group of Israeli Arabs.[208] The frequencies of whorls, loops, and arches on each of the ten fingers were examined in 500 males of each group, particular care being taken to avoid including members of the same family. For each population, data on 5000 fingers were collected. The mean values for the frequencies of whorls and loops in the Jewish populations from different countries were found to be very similar. The average values for all Jewish communities are also quite close to the average for Israeli Arabs but very different from the figures reported for the British population[67] (see diagrams for whorls and loops).

For comparison with other non-Jewish groups there is a considerable amount of data available in the literature in the form of a pattern index. This index is assumed to reflect the total frequencies of whorls, loops, and arches in the population, and it is obtained by adding the frequency of loops to twice the frequency of whorls and dividing by 10 if the frequencies are in the form of percentages.[67]

The data on pattern indices of Jews and a variety of non-Jewish populations in Europe, North America, and the Middle East have been compiled in the form of a diagram. Whereas the non-Jews from Europe and North America have indices ranging from 11.85 to 12.59, none of the Jewish populations, even those who had their domicile for long periods in these same countries, have such low indices. The indices for the various Jewish groups range between those of Italians on one hand and Israeli Arabs and Egyptian Copts on the other.

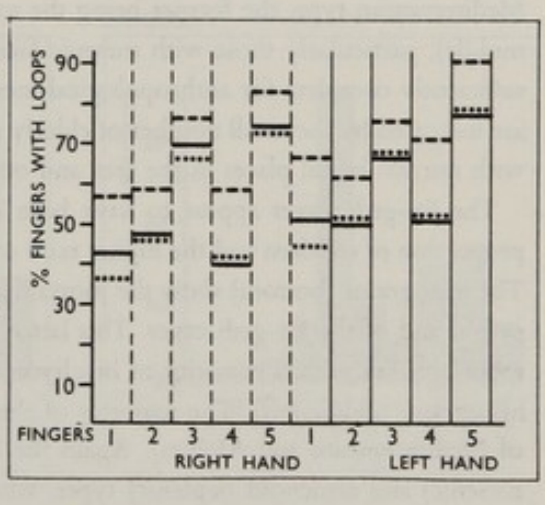
The similarity of pattern indices among Jews and populations such as Egyptian Copts may be attributable to their Eastern Mediterranean origin. Thus even Jewish groups which have resided for long periods of time in Europe and North America exhibit some evidence of their origin from what may be called an "Eastern Mediterranean gene pool."



WHORL FREQUENCIES

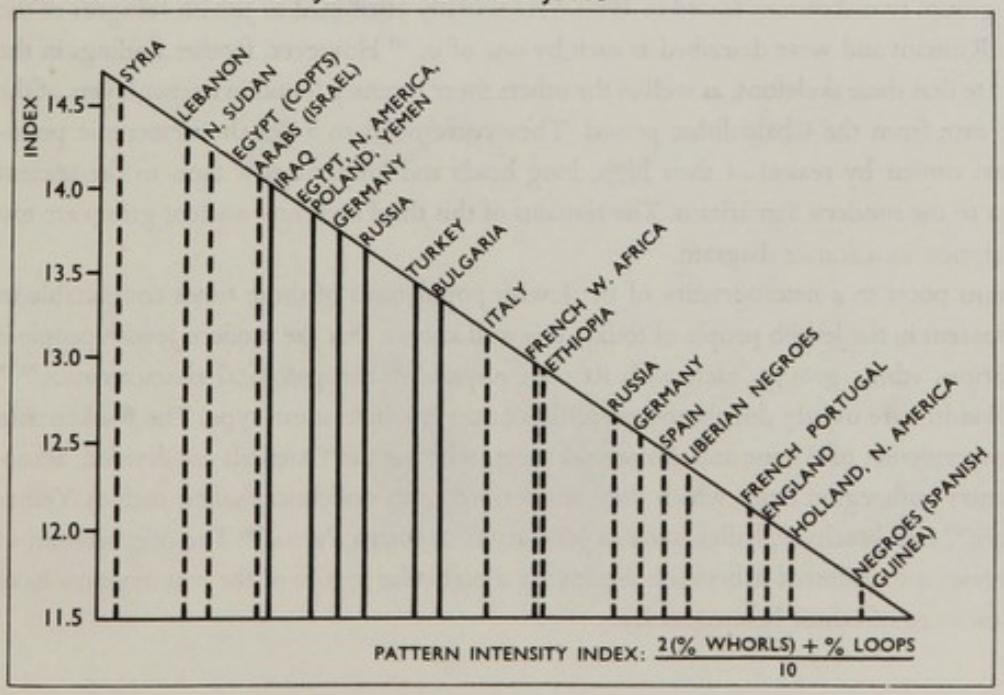
ENGLISH
JEWS
ARABS

LOOP FREQUENCIES



ENGLISH
JEWS
ARABS

PATTERN INDICES OF JEWS AND NON-JEWS



NON-JEWS
JEWS

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DURING THE various expeditions to the Judean Desert organized since 1955 by the Department of Antiquities, the Israel Exploration Society, and the Hebrew University, a number of human skeletons have been found. These may be divided into three principal groups according to the location in which they were found and the periods to which they have been attributed.

Forty-nine skeletons in all, from the period of Bar Kokhba (second century A.D.) were found by Aharoni in the "Cave of Horror" of Nahal Hever[6, 180] and in the Cave of Nahal Seelim[7] and by Yadin in the "Cave of Letters" of Nahal Hever.[266] A second group includes 81 skeletons found by Avigad and 10 skeletons found by Yadin in the Caves of En-gedi.[25] They probably belong to a Jewish population living in the first or second century B.C. The third group consists of 9 skeletons found by Bar-Adon in the Caves of Nahal Mishmar[26, 181] and of one found by Aharoni in the "Cave of Horror." These appear to date back to the Chalcolithic period.

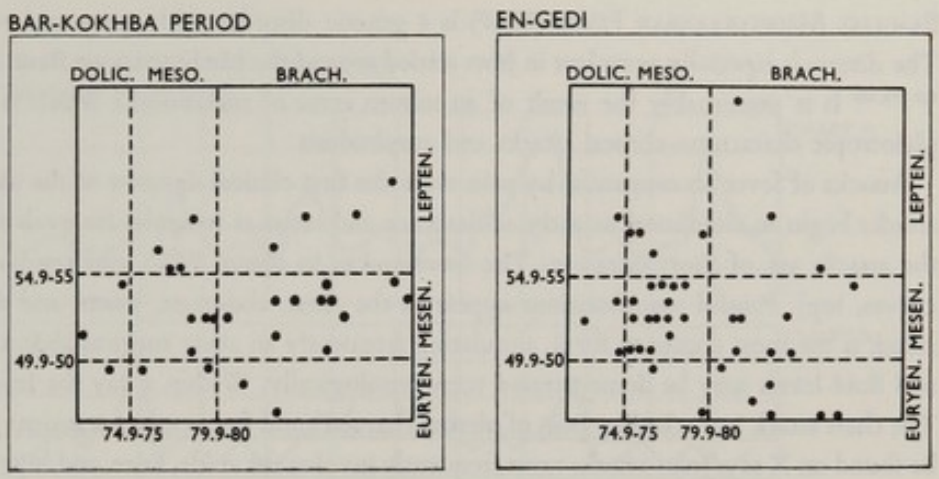
The group of the Bar Kokhba period probably represents the remnants of Jewish families who took refuge in these caves during the war against the Romans (A.D. 133-135) (see p. 10). This population comprises mainly brachycephalics of the Alpine-Armenoid types and dolichomesocephalics of the Mediterranean type, the former being the most prevalent (see scatter diagram, top, and histogram, middle), particularly those with mesenic faces. The diagrams refer only to those skulls which were sufficiently complete for anthropological measurements. The unnatural circumstances of their death are indicated by the small number of elderly people and the high proportion of children as compared with normal burial places in the area and other regions of those times.[11]

The En-gedi caves appear to have been used as a cemetery for the En-gedi village, the lower proportion of children and the higher ratio of adults corresponding to those of a normal burial place. The histograms (bottom) show the mortality by age groups of the population from the Bar Kokhba period and of the En-gedi caves. This latter population is characterized by a clear predominance of mesocephalics with a minority of brachycephalics and dolichocephalics (scatter diagram, top right; histogram, middle left). The majority of the mesocephalics are mesenic (possibly due to admixture of Mediterraneans and Alpines). Again the brachycephalics appear to belong to the Alpine (eurymesenic) and armenoid (leptenic) types, whereas the dolichocephalics are probably Mediterraneans (sensu lato). This material is still under study, and typing is incomplete.

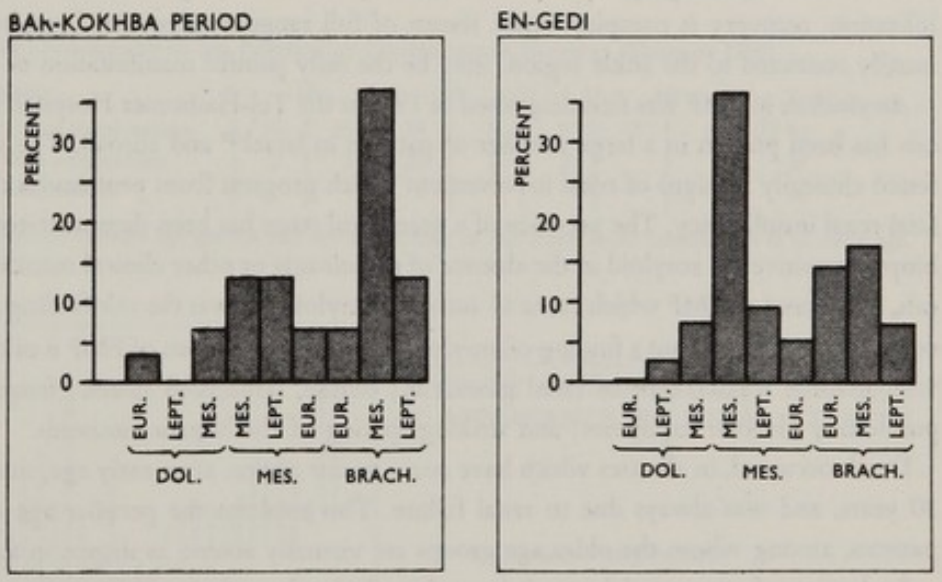
Of the third group, two skeletons found in 1960 were initially attributed to Jewish refugees of the war against the Romans and were described as such by one of us.[181] However, further findings in the same cave indicate that these skeletons, as well as the others more recently found in deeper layers of the cave, probably date from the Chalcolithic period. They correspond to a dolichomesocranic population, somewhat similar by reason of their high, long heads and long, narrow faces to the ancient Corded types or to the modern Samaritans. The remains of this third and most ancient group are too scanty for description in a scatter diagram.

These variations point to a heterogeneity of the Jewish populations of those times comparable to that which is apparent in the Jewish people of today. It is well known that the modern Jewish people is divided into various ethnic groups, each with its own physical anthropological characteristics.[65, 73, 85, 137, 161] The Sephardim are mostly dolichomesocephalics of the Mediterranean type. The Ashkenazim are mainly brachycephalics of Alpine and Armenoid types, whereas the Orientals are divided, according to the country and region from which they are derived, into dolichocephalics, such as Yemenites[258] and Iraqis,[259] and brachycephalics, such as Jews from northern Persia.[260] The organization of the ancient Hebrews into different tribes each occupying a particular region of the country may have reflected some measure of ethnic heterogeneity.

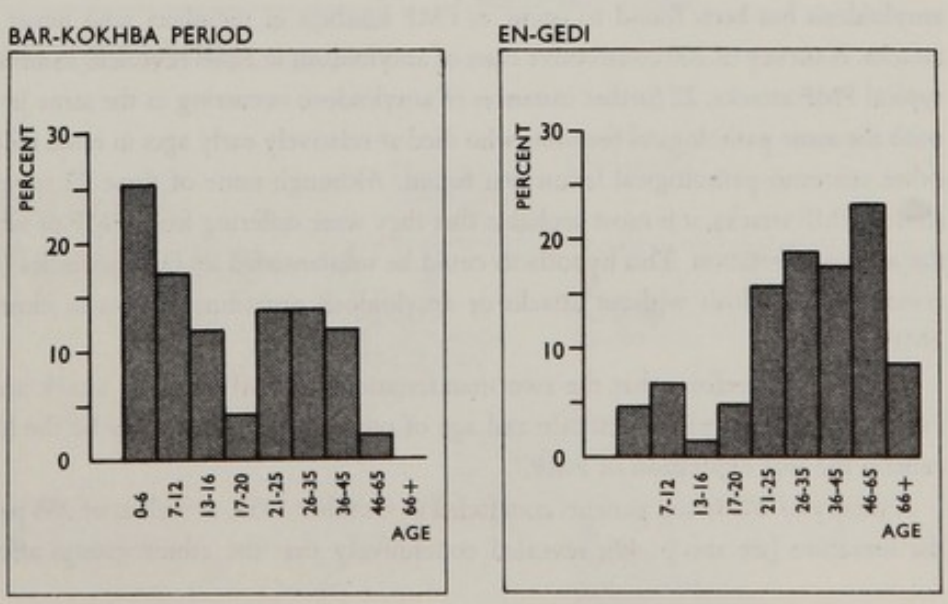
SCATTER DIAGRAM OF CRANIAL AND FACIAL INDICES



DISTRIBUTIONS OF CRANIAL INDICES



MORTALITY BY AGE GROUPS



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Familial Mediterranean Fever (FMF) is a genetic disorder with autosomal recessive inheritance. The disease is especially prevalent in Jews settled around the Mediterranean Basin and in Armenians.[31, 122, 159, 228] It is presumably the result of an inborn error of metabolism which is manifested by two pleiotropic characters—clinical attacks and amyloidosis.

Attacks of fever accompanied by pain were the first clinical signpost of the disease. Usually, these attacks begin in childhood or early adolescence and recur at irregular intervals thereafter. As a rule, the attacks are of short duration. The fever spikes to about 39°C. and resolves rapidly (see fever curves, top). Painful manifestations appear in the chest, abdomen, joints, and skin. The abdominal attack is the most common form, simulating frequently an acute surgical abdomen; intestinal atony and fluid levels may be demonstrated roentgenologically. Within a day the fever and pain subside. The chest attack is marked by pain of pleural character and frequently a transient pleural effusion may be found on X ray. Joint attacks most frequently involve the ankle, knee, and hip, usually presenting as an acute monoarthritis. Although joint attacks are as a rule short lived, they sometimes take a long and chronic course. It is highly characteristic that in spite of massive joint effusion and prolonged immobilization, recovery is complete, with return of full range motion. An "erysipelas like-erythema," usually restricted to the ankle region, may be the only painful manifestation of an attack.

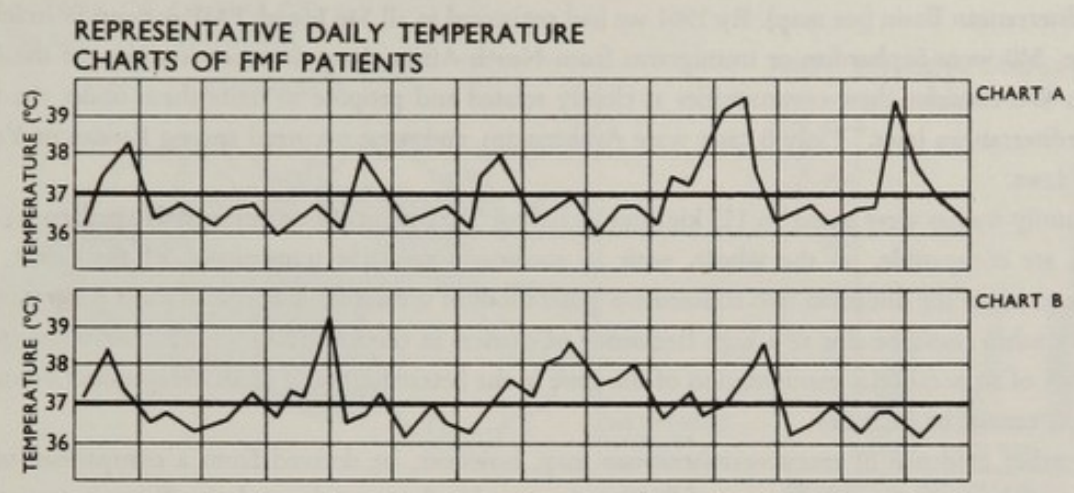
Amyloidosis in FMF was first diagnosed in 1951 at the Tel-Hashomer Hospital. Since then amyloidosis has been proven in a large number of patients in Israel[123] and abroad. The amyloidosis is manifested clinically by signs of renal involvement which progress from proteinuria through nephrosis to fatal renal insufficiency. The presence of a preclinical stage has been demonstrated by renal and rectal biopsies positive for amyloid in the absence of proteinuria or other clinical manifestations of amyloidosis. In all cases of FMF which came to autopsy, amyloidosis was the *sole* finding; no case of FMF has come to autopsy without a finding of amyloidosis. The amyloidosis of FMF is of the perireticular type with massive replacement of renal glomeruli; diffuse, lardaceous spleen; frequent involvement of pulmonary alveolar capillaries; and striking sparing of the hepatic sinusoids.

Death occurred, in all cases which have come to our notice, at an early age, usually between 10 and 30 years, and was always due to renal failure. This explains the peculiar age distribution of FMF patients, among whom the older age groups are virtually absent, as shown in the table (right).

Evaluation of our material revealed a striking lack of correlation among the age of onset, number, duration, and severity of FMF attacks, and the appearance of amyloidosis (see diagram right). Further, amyloidosis has been found to occur in FMF kinships in members who never experienced clinical attacks. A survey of 200 consecutive cases of amyloidosis in Israel revealed, in addition to 36 cases with typical FMF attacks, 22 further instances of amyloidosis occurring in the same Jewish groups as FMF, with the same pathological features, who died at relatively early ages in renal failure and in whom no other anatomo-pathological lesion was found. Although none of these 22 subjects had experienced clinical FMF attacks, it is most probable that they were suffering from FMF of which amyloidosis was the sole manifestation. This hypothesis could be substantiated by family studies (see pedigrees) which revealed amyloidosis without attacks or amyloidosis preceding attacks in close relatives of typical FMF patients.

It appears, therefore, that the two manifestations of FMF—clinical attack and amyloidosis—vary rather independently in penetrance and age of onset and that each may be the first to appear or may remain the sole expression of FMF.

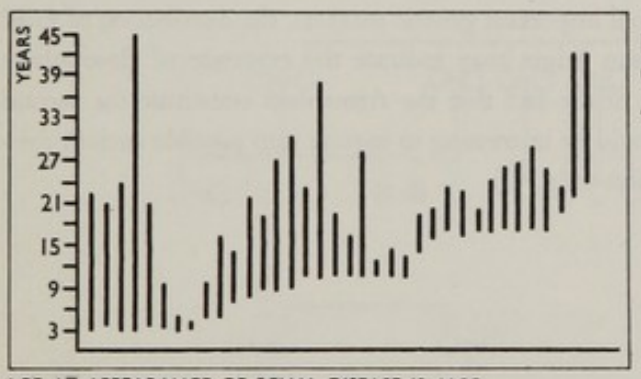
A survey of 262 Israeli patients concluded in October 1959, as well as of 258 patients collected from the literature (see also p. 40), revealed conclusively that the ethnic groups affected derive from the



Age Distribution of 141 Patients at Tel-Hashomer Hospital (Series of 1959)

Age in years	0	10	20	30	40	50	60	70	*Total*
Without renal involvement	16	25	39	5	5	3	1		94
Living, with amyloidosis	2	3	20	7	3				35
Died of amyloidosis		4	8						12

Note the scarcity of patients in older age groups and the appearance of and death from amyloidosis at an early age.



AGE AT APPEARANCE OF RENAL DISEASE IS ALSO INDEPENDENT OF NUMBER AND SEVERITY OF FMF ATTACKS

LACK OF CORRELATION BETWEEN AGE OF ONSET OF FMF ATTACKS AND AGE AT APPEARANCE OF RENAL ATTACKS

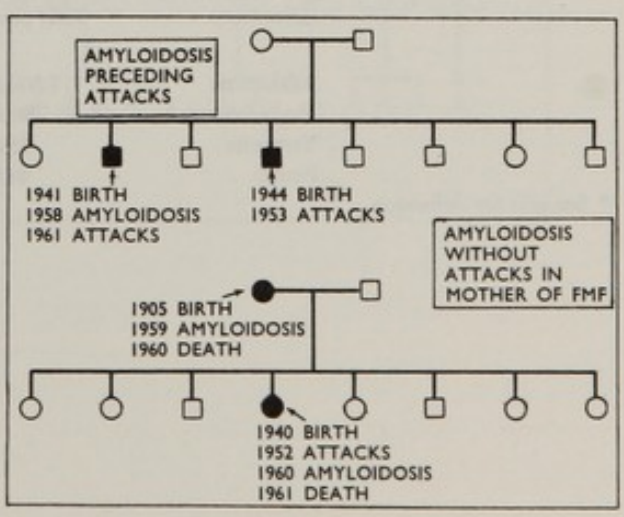
EACH BAR— ONE PATIENT

AGE AT DIAGNOSIS OF NEPHROPATHY

AGE AT FIRST ATTACK

AMYLOIDOSIS

MAY APPEAR WITHOUT ATTACKS OR PRIOR TO ATTACKS IN FMF KINSHIP



AFFECTED

HEALTHY

REPRESENTATIVE PEDIGREES

Mediterranean Basin (see map). By 1961 we had registered in all 346 Jewish FMF patients in Israel. Of these, 340 were Sephardim or immigrants from North Africa, Iraq, or other countries of the Near East. We consider these communities as closely related and propose to unite them under the term "Mediterranean Jews." Only 6 cases were Ashkenazim, and none occurred among Persian or Yemenite Jews.

Family studies were based on 113 kinships including 232 patients (see representative pedigrees). The data are compatible, on the whole, with an autosomal recessive transmission of the defect. The appearance of the disease in two consecutive generations of several families and in three generations of one kinship could be due to a high frequency of carriers in certain local foci. The alternative possibilities of an occasional manifestation of the gene in the heterozygote or of an independent dominant defect cannot be excluded.

Further evidence of recessive inheritance may, however, be derived from a comparison of the consanguinity rates among parents of FMF patients and in the general population[103] (see histogram) of each ethnic group.

The population of Israel comprises at present approximately 1,000,000 Ashkenazim, whereas the Sephardim and the various immigrant groups from Oriental countries around the Mediterranean Basin constitute about 700,000. The crude incidence rates of FMF differ very significantly between these two population sectors (see table). This difference would become more pronounced by a correction accounting for the age stratification of the various communities. Especially in the Oriental communities a large proportion of individuals are young children, in some of whom FMF may become manifest during later childhood and adolescence.

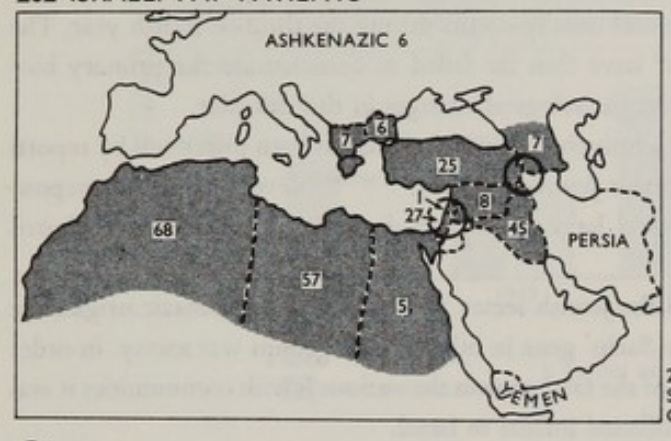
Since rare recessive genes should be considered important genetic markers, the distribution of FMF among various Jewish groups of Mediterranean origin may indicate the existence of close ethnic affinities between these communities. In view of the fact that the Armenians constitute the second ethnic group in which FMF is prevalent, it would be interesting to inquire into possible ancient connections of these two peoples (see also discussion on p. 40).

PREVALENCE OF FMF AMONG JEWISH GROUPS IN ISRAEL, 1961

Community	*Total population*	*Number FMF patients*
Ashkenazic	1,000,000	6
Mediterranean*	700,000	340
Yemenite	75,000	0
Persian	40,000	0

* See text for definition.

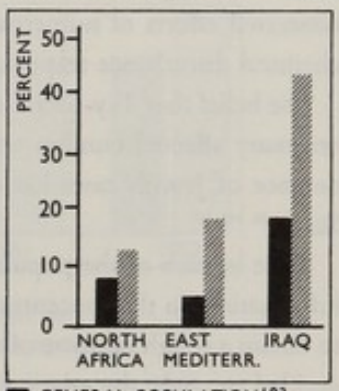
COUNTRIES OF ORIGIN OF
262 ISRAELI FMF PATIENTS



262 PATIENTS —
SERIES OF
OCTOBER 1959

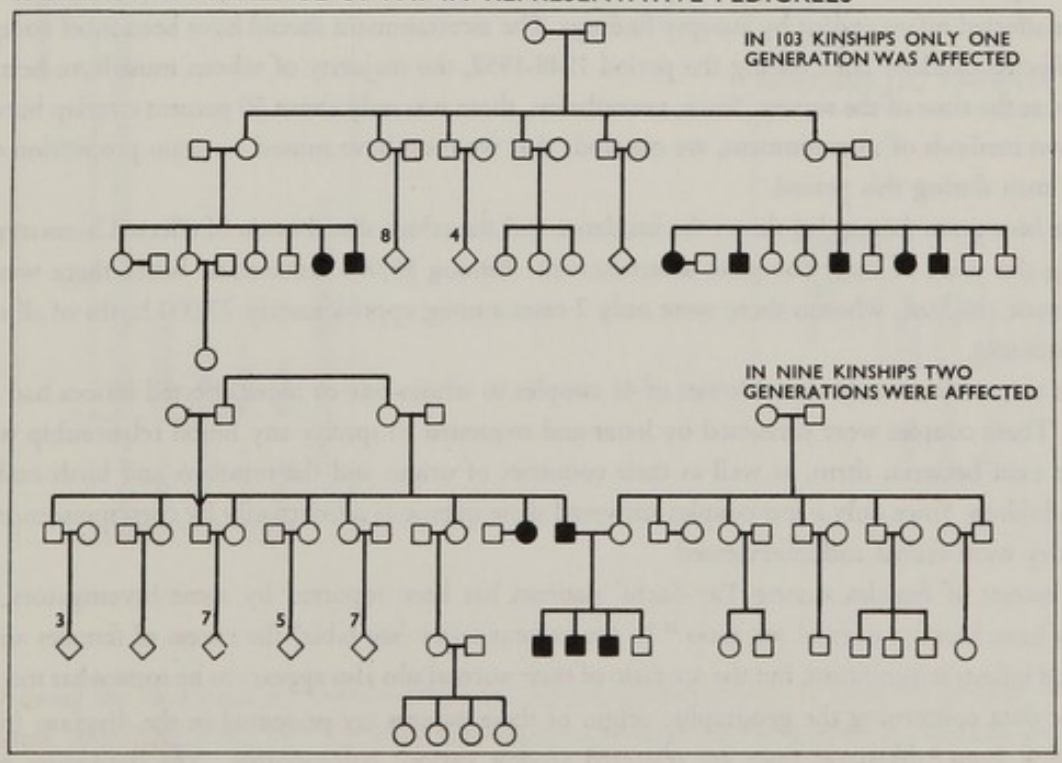
○ ARMENIAN AND JEWISH FOCI

FIRST COUSIN MARRIAGES



■ GENERAL POPULATION[103]
▨ PARENTS OF FMF PATIENTS

FAMILIAL OCCURRENCE OF FMF IN REPRESENTATIVE PEDIGREES



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TAY-SACHS' DISEASE, or infantile amaurotic idiocy, is a recessive disorder characterized by lipid storage in the ganglion cells of the C.N.S. The affected infants undergo a prolonged process of neural and mental degeneration. Death is inevitable and usually occurs during the third or fourth year. The concerted efforts of numerous investigators[23] have thus far failed to demonstrate the primary biochemical disturbance responsible for the overt pathological changes in this disorder.

The belief that Tay-Sachs' disease occurs exclusively in Jewish infants has been disproved by reports on many affected families without any traceable Jewish ancestry.[118, 141, 145] Nevertheless, the preponderance of Jewish cases has emerged in several large surveys made in Europe and in the United States.[22, 141, 145]

Since in each of the populations surveyed the Jewish sector was largely of Ashkenazic origin, the information on the concentration of the Tay-Sachs' gene in other Jewish groups was scanty. In order to obtain a rough estimate of the frequencies of the fatal gene in the various Jewish communities it was decided to study the ethnic distribution of affected infants in Israel.

The survey was made in 1954-55. Two independent methods of ascertainment were employed. Letters were sent to all registered pediatricians in Israel and also to the pediatric wards of the large hospitals and to the institutions for incurable children, requesting names and addresses of patients suffering from Tay-Sachs' disease. The Death Register of the Central Bureau of Statistics was scanned for cases of infants who had succumbed to this disease. (The help of Dr. Gertrude Kallner, who gave us access to this Register, is gratefully acknowledged.) None of the cases ascertained by either method was accepted unless confirmed by an ophthalmologist who had seen the cherry-red spot in the macula of the affected infant and/or by autopsy findings. The ascertainment should have been most complete for affected children born during the period 1948-1952, the majority of whom must have been deceased at the time of the survey. Since, nevertheless, there was only about 50 percent overlap between the two methods of ascertainment, we conclude that we must have missed a certain proportion of all cases born during this period.

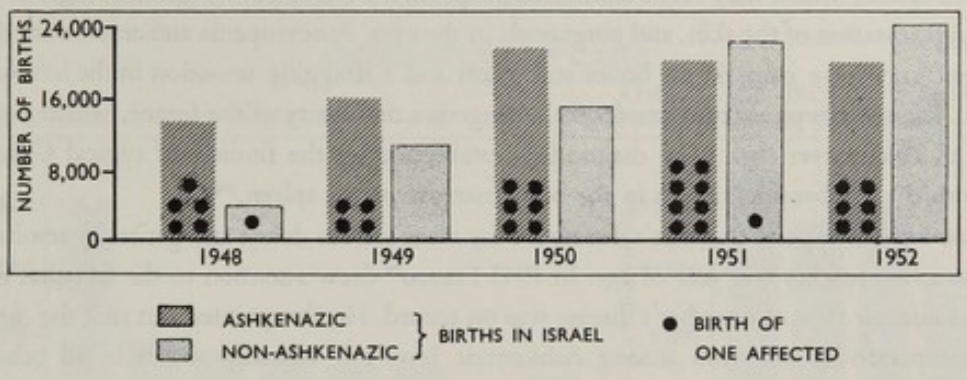
The histogram (top right) shows the incidence and the ethnic distribution of affected homozygotes during the years of most complete ascertainment. Among 85,000 Ashkenazic births there were 29 amaurotic children, whereas there were only 2 cases among approximately 77,000 births of all other communities.

We were able to trace the addresses of 41 couples to whom one or more affected infants had been born. These couples were contacted by letter and requested to specify any blood relationship which might exist between them, as well as their countries of origin and the numbers and birth ranks of their children. Since only a few couples answered these questions satisfactorily by correspondence, the majority were visited and interviewed.

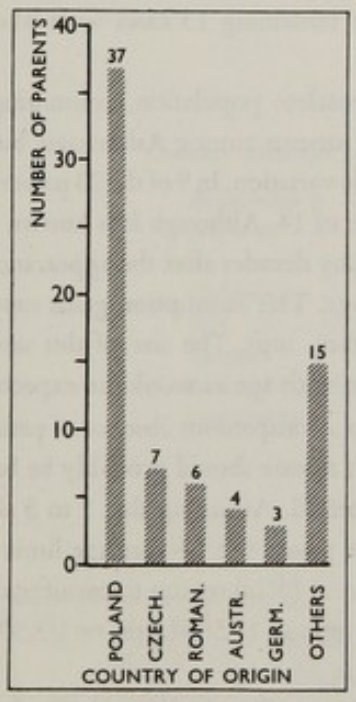
An excess of females among Tay-Sachs' patients has been reported by some investigators;[118, 141] others have found a normal sex ratio.[22] In the present series (see table) the excess of females among affected infants is significant, but the sex ratio of their normal sibs also appears to be somewhat too low.

The data concerning the geographic origin of these parents are presented in the diagram (right). The few non-Ashkenazic cases are scattered among various communities. The derivation of the Ashkenazic parents of our sample neither confirms nor refutes the claim[22] that the disease has spread from a focus which is assumed to have been located in eastern Europe. It is true that only a few parents originated in western European countries such as Germany. But it should be remembered that German Jewry constitute a small proportion of Israel's Ashkenazim. Nevertheless, the distribution of the disease is probably heterogeneous, and gene frequency estimates may be subject to large errors (see also pp. 176-183).

TAY-SACHS CASES AMONG ASHKENAZIC AND NON-ASHKENAZIC BIRTHS OF SEVERAL YEARS



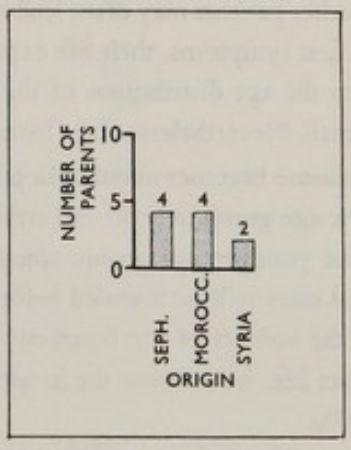
ORIGIN OF 72 ASHKENAZIC PARENTS



DISTURBED SEX RATIO IN 41 AFFECTED SIBSHIPS

	Boys	*Girls*
Normal	13	17
Affected	17	32
Total	30	49

ORIGIN OF 10 NON-ASHKENAZIC PARENTS



Among the 36 Ashkenazic couples who had affected children, three, or about 10 percent, were first cousins. Assuming a rate of 1.5 percent first-cousin marriages for the general Ashkenazic population (see p. 341) we arrive by Dahlberg's formula at an estimate of $q = 1/100$ for the frequency of the Tay-Sachs' gene in the Ashkenazic sector of Israel's population. A calculation based on the incidence of homozygotes among all births yields a somewhat higher estimate ($q = 1/60$). An independent estimate of $q = 100$ has recently been obtained[145] for the Ashkenazic Jews of New York City.

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THE CHRONIC ADULT TYPE of Gaucher's disease may become overt in childhood or much later, the severity of the manifestations varying from case to case.[88, 105, 246] The most striking feature is enlargement of the spleen, which may reach enormous proportions. Other pathological changes are hepatomegaly, pigmentation of the skin, and pinguecula in the eyes. Pancytopenia and anemia are common. The patient may have pains in his bones and joints and a dragging sensation in the left side of the abdomen. The most typical roentgenological change is a deformity of the femur, which assumes the shape of an Erlenmeyer flask. The diagnosis is established by the finding of typical Gaucher cells loaded with the cerebroside kerasin in the bone marrow or the spleen.[106]

The *acute infantile* type of Gaucher's disease is a far more serious defect and generally results in death before the infant reaches one year of age. In 1943 Franco[89] drew attention to the fact that no Jewish case of the *infantile* type of Gaucher's disease was on record. He also pointed out that the *chronic adult* type is comparatively common among Ashkenazic Jews but virtually absent in all other Jewish communities.

The present study deals with 23 patients suffering from the *chronic adult* type. The patients were identified by a search of hospital files and by correspondence with physicians. An attempt was made to identify all patients who lived in Jerusalem in 1957.[94] This search revealed ten cases, all of whom belonged to the Ashkenazic community (see diagram, top). The remaining 13 cases were also of Ashkenazic origin.

The crude prevalence rate for the Ashkenazic sector of the Jerusalem population, amounting to 1/6200, is probably lower than the incidence of potential Gaucher patients among Ashkenazic births. The age of onset (diagram, bottom right) of the disease exhibits a wide variation. In 9 of the 23 patients of the present series the first symptoms became manifest after the age of 14. Although it is known that Gaucher patients may often lead comparatively normal lives for many decades after the appearance of the first symptoms, their life expectancy may well be below average. This assumption gains support from the age distribution of the ten Jerusalem patients (see diagram, top). The size of this sample is small. Nevertheless it is of interest that the prevalence fails to rise with age as would be expected if the disease becomes manifest in previously latent cases. There is also a conspicuous absence of patients in the age group over 60. An estimate of the incidence of Gaucher's disease should probably be based on the youngest age group, among whom 3/17,500 cases were detected. Assuming that 1 to 3 additional cases will be revealed before all members of this group have passed the 14-year age limit and that the number of 4 to 6 patients will be increased by about 40 percent (9/23) owing to manifestation in later life, we estimate the incidence of potential patients at 5 to 9 among 17,500 births or 1/3,500 to 1/2,000.

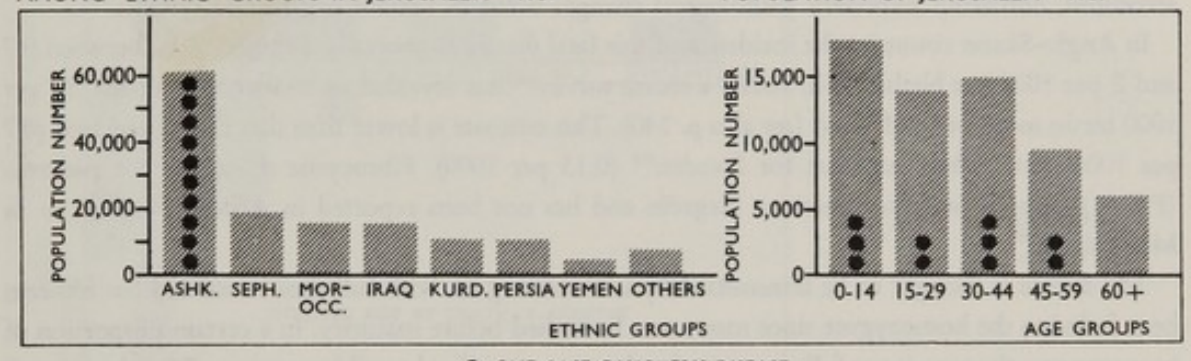
The table (center) summarizes the available information on the incidence of Gaucher's disease in the close relatives of our 23 propositi. (see also representative pedigrees, bottom). These data do not lend themselves to any simple Mendelian interpretation. It should be noted that in spite of the variability in age of onset, the risk for sibs of propositi is somewhat higher than the risk of parents. However, the difference is not significant. Similarly, the occurrence of one cousin union among 23 parental couples (0.043 ± 0.043) gives no clue to recessive inheritance in a population with 1.5 percent first-cousin marriages (see also p. 341), especially since other workers[105] have also stressed that Gaucher patients are usually born to unrelated parents. More comprehensive family studies will be required before one can reject or accept the hypothesis that Gaucher's disease is transmitted by a dominant gene with incomplete penetrance. *

* The authors are greatly obligated to Dr. O. Schmelz, Statistical Bureau, Government of Israel, for demographic data regarding the Jerusalem population.

DISTRIBUTION OF CASES

AMONG ETHNIC GROUPS IN JERUSALEM—1957

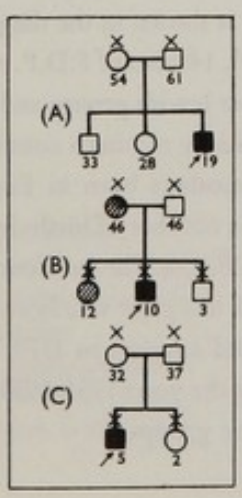
AMONG AGE GROUPS IN ASHKENAZIC POPULATION OF JERUSALEM—1957



● ONE CASE GAUCHER'S DISEASE

OVERTLY AFFECTED AND "SUSPECTED" CASES AMONG CLOSE RELATIVES OF PROPOSITI

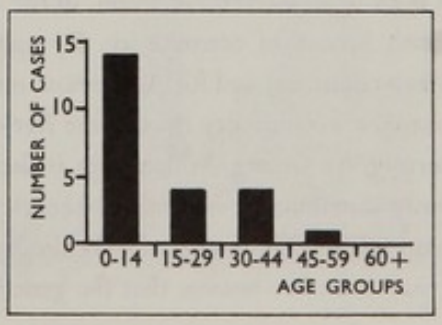
Relationship to propositus	*Total number known*	*Number affected*	*Number suspected*	*Affected and suspected*	
				Number	%
Children	23	—	—	—	—
Sibs	39	2	4	6	15.4
Parents	46	—	2	2	4.4
Aunts and uncles	64	1	—	1	1.6
Grandparents	38	1	1	—	2.6



REPRESENTATIVE PEDIGREES

● AFFECTED
⊗ SUSPECTED
× EXAMINED
↗ PROPOSITUS
46 AGED 46

AGE OF ONSET IN 23 CASES



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FIBROCYSTIC DISEASE OF THE PANCREAS, or Mucoviscidosis, is a hereditary systemic disease in which most or all of the exocrine glands of the body have abnormal secretions. Owing to these abnormal secretions, numerous secondary pathological changes occur in various organs and systems.[10]

In Anglo-Saxon countries the incidence of this fatal disease is generally assumed to be between 0.7 and 2 per 1000 live births.[216] However, a recent survey[230] has revealed an incidence of only 0.27 per 1000 births in the state of Ohio (see also p. 140). This estimate is lower than that for Switzerland (0.7 per 1000) but higher than that for Sweden[216] (0.13 per 1000). Fibrocystic disease of the pancreas (F.D.P.) is rarely seen in American Negroes and has not been reported in African Negroes or in Mongolians.[75]

The disease is thought to be transmitted by a recessive gene with full penetrance and has hitherto been lethal to the homozygote since most cases have died before maturity. In a certain proportion of homozygotes the gene is not fully recessive but becomes manifest by mild symptoms.[75] Lately, because of the finding of adult cases with F.D.P., it has been suggested that the basic defect may be transmitted as an autosomal dominant character.[144]

Prior to 1955, F.D.P. was rarely diagnosed in Israel. At that time the disease was believed to be uncommon among Jewish children. Since 1955, however, several typical cases of this condition have been reported from various hospitals in Israel, mainly because of the availability of a simple diagnostic test—the finding of increased amounts of sodium and chloride in the sweat of affected persons.

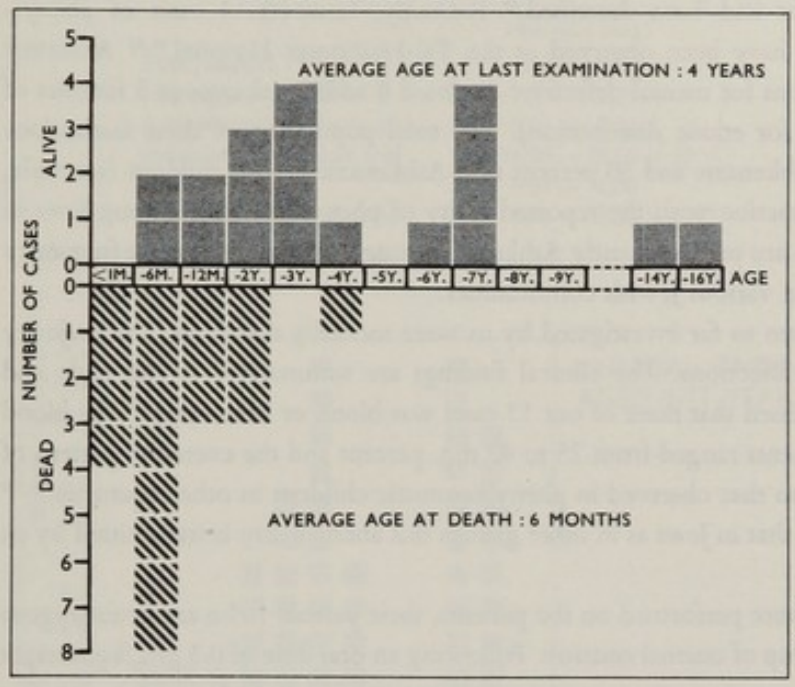
The present study was conducted in 1960-61. Questionnaires were sent to the heads of all pediatrics and pathology departments in Israeli hospitals in order to determine the incidence and nature of F.D.P. in the country. Reports were received from every hospital and included clinical and pathological studies.

Thirty-eight of the reported cases were accepted as F.D.P. The diagram (top) shows the age distribution of these cases at the last examination or at death. In 17 of the 19 deceased cases the diagnosis had been confirmed by autopsy. Meconium ileus had been found in four (10%) of these subjects.

The table (center) summarizes the results of sweat tests performed on all affected subjects. It is of interest that the electrolyte secretion of one of these children was within the normal range.

The distribution of the 38 cases by year of birth and by population sector is shown in the diagram (right bottom). During the years of most complete ascertainment (1955-1959), 14 cases of F.D.P. were born in the Ashkenazic community, whereas only 10 cases occurred in all other Jewish groups and one was born to an interethnic union. In the official statistics[18] the births are classed by mother's continent of birth instead of community. By applying a correction for Sephardic mothers born in Europe (Balkan countries) and for Ashkenazic mothers born in Israel, we estimate the number of births in the Ashkenazic community during the five-year period under study at about 68,000. The incidence of homozygotes among Ashkenazim is therefore estimated as 0.2 per 1000. If the gene was homogeneously distributed over the Ashkenazic community its frequency (q) would amount to 1/70. The Ashkenazic births constituted only about one-third of all Jewish births during the years 1955-1959 and we may therefore assume that the gene is much rarer in the non-Ashkenazic groups.

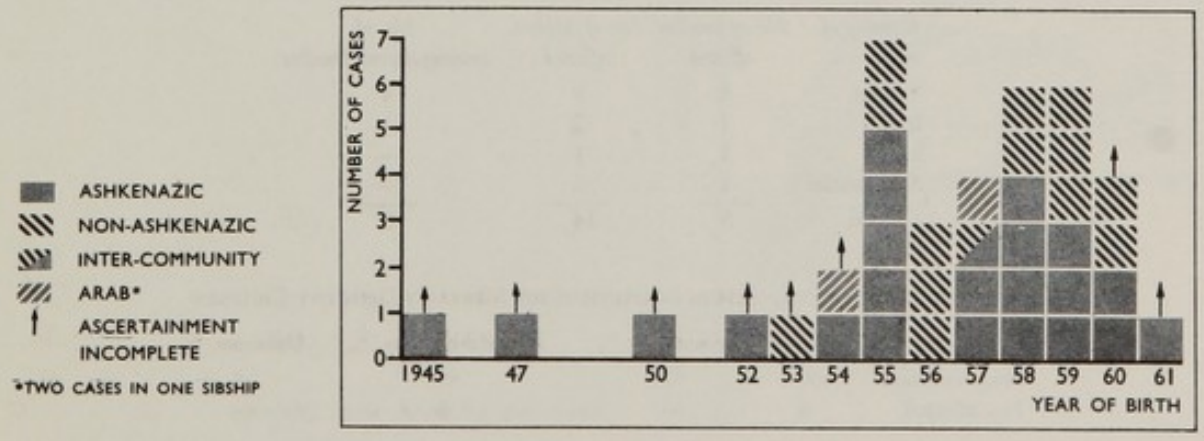
VIABILITY DATA ON 38 CASES OF F.D.P



Sweat Tests of Affected Subjects

	No. of individuals
Na^+ and/or Cl^- > 60 m Eq/l	20
< 60 m Eq/l	1
Means: Na^+: 104 m Eq/l	
Cl^+: 108 m Eq/l	
Normal range: Na^- < 60 m Eq/l	
Cl^- < 60 m Eq/l	

INCIDENCE IN ISRAEL



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Kaplan Hospital
Rehovoth, Israel

PHENYLKETONURIA has been considered very rare among Jews, because until recently only one Jewish family with this disorder had been described.[63] Recently, however, 4 cases of phenylketonuria in Yemenite children have been observed at the Tel-Hashomer Hospital.[61,62] A survey among 1000 children in institutions for mental defectives disclosed 8 additional cases in 5 families of oriental Jews (see table, below, for ethnic distribution). The total population of these institutions consisted of about 50 percent Ashkenazic and 50 percent non-Ashkenazic Jewish children (see table, below). These findings, in conjunction with the reported rarity of phenylketonuria among Jews in Europe and North America who are predominantly Ashkenazic, suggest differences in the frequency of this abnormal gene among the various Jewish communities.

All the phenylketonuric children so far investigated by us were mentally defective. The majority showed EEG changes and skin affections. The clinical findings are summarized in the table and diagram (right). It should be stressed that none of our 13 cases was blond or blue-eyed.[66] The blood phenylalanine levels of these patients ranged from 25 to 40 mg. percent and the excretion pattern of urinary metabolites was similar to that observed in phenylketonuric children in other countries.[53,132] Pedigree studies have confirmed that in Jews as in other groups this abnormality is transmitted by an autosomal recessive gene.

Phenylalanine tolerance tests were performed on the patients, their parents (who are heterozygous for the defective gene), and a group of normal controls. Following an oral dose of 0.3 gm./kg. weight of DL phenylalanine, the blood tyrosine concentration was determined at 0, 2, 4, and 6 hours after administration of the drug. For the majority of the heterozygotes the curves thus obtained (see right bottom) fall below those of the normal controls, but there is, nevertheless, a certain overlap. It remains to be seen whether this test will prove superior to others,[254] all of which have failed so far to detect the heterozygote with 100-percent certainty.[133,257]

In view of the high cost of L phenylalanine and the encouraging preliminary results obtained with DL phenylalanine as a loading compound, further experimentation with this method of detecting heterozygotes is indicated.*

ETHNIC DISTRIBUTION OF ALL CASES OF PHENYLKETONURIA DIAGNOSED BY TEL-HASHOMER TEAM

Country of origin	*No. of families affected*	*No. of children affected*	*No. of consanguineous families*
Yemen	6	9	4
Iraq	1	2	1
Iran	1	1	—
Afghanistan	1	2	—
Total	9	14	5

SURVEY OF PHENYLKETONURIA IN INSTITUTIONS FOR MENTALLY DEFECTIVE CHILDREN

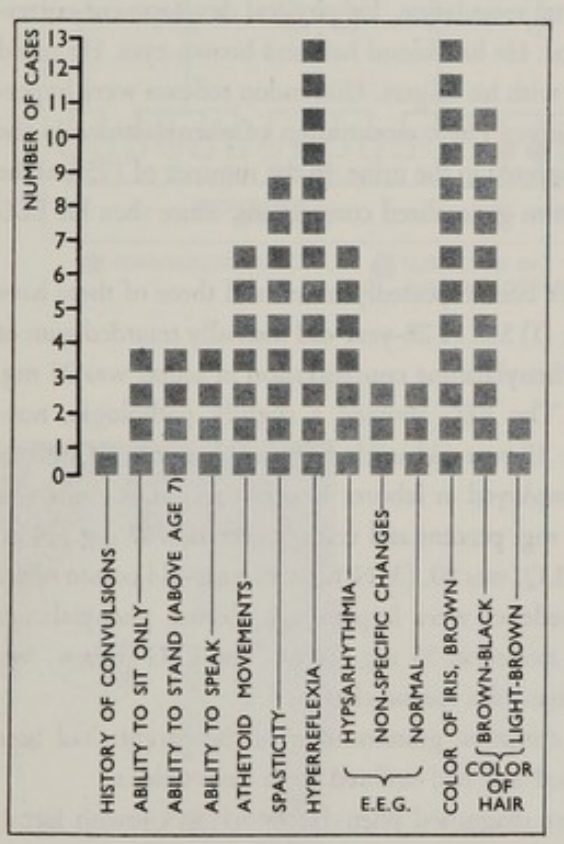
	Total	*Ashkenazim, %*	*Non-Ashkenazim, %*	*Unknown, %*
No. examined	950	47	49	4
No. affected	6	—	6	—

* This investigation has been aided by a grant from the Rockefeller Foundation (RF 60101).

EXCRETION OF URINARY METABOLITES† IN 13 CASES OF PHENYLKETONURIA AND IN NORMAL SUBJECTS

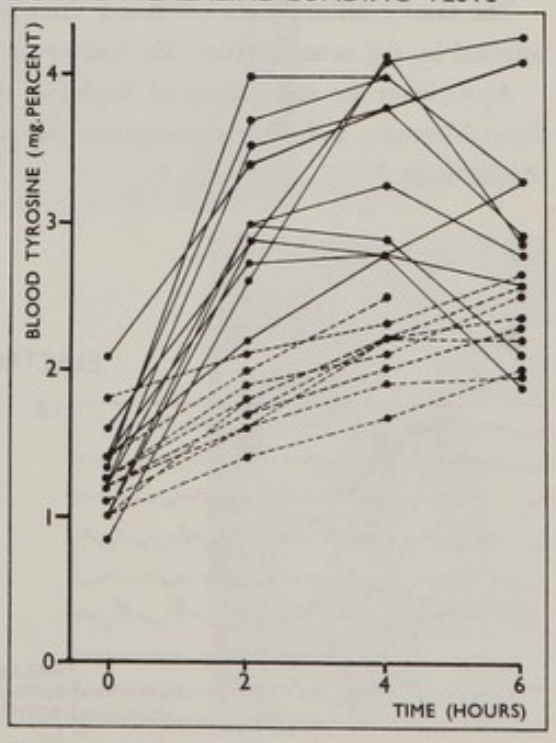
	Phenylketonurics	*Normals*
Phenylalanine	0.20 — 0.30	
Phenylpyruvic acid	0.70 — 1.75	
6-Hydroxyphenyllactic acid	0.10 — 0.20	
Indolacetic-Indollactic acid	18.00 — 20.00 × 10^{-3}	4.00 — 8.00 × 10^{-3}
Indican	0.08 — 1.00	0.02 — 0.25
5-Hydroxyindolacetic acid	1.90 — 3.50 × 10^{-3}	3.00 — 8.00 × 10^{-3}

† All concentrations are indicated in mg./mg. creatinine.



CLINICAL FINDINGS IN 13 CASES AGED 2-17 YEARS

BLOOD TYROSINE LEVELS DURING DL PHENYLALALINE LOADING TESTS



LOADING DOSE: 0.3 mg./kg. body weight

—— NORMAL CONTROLS

---- HETEROZYGOTES

A. Szeinberg, B. E. Cohen, H. Boichis, S. Pollack, E. Bodonyi, N. Hirshorn, R. Bar-Or
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PHENYLKETONURIA—a biochemical lesion with recessive inheritance—is responsible for about 1 percent of all mental deficiency in Britain. It is virtually absent[63] in European and American Jews but has recently[61, 152] been described in several Oriental Jewish communities. The clinical manifestations of this disease, including its effects on mental ability, exhibit a wide range of variation, which has been extensively studied in affected subjects of Anglo-Saxon extraction.[119, 190] Since the expressivity of phenylketonuria on a rather different ethnic background is of considerable interest, the clinical condition of four affected subjects belonging to a Jewish family from Iraq will be described in detail.

In June 1958, I.E., a 2½-year-old boy (see photograph, right center) with mental and motor retardation was referred to our clinic for evaluation. The parents were first cousins (see pedigree, right).

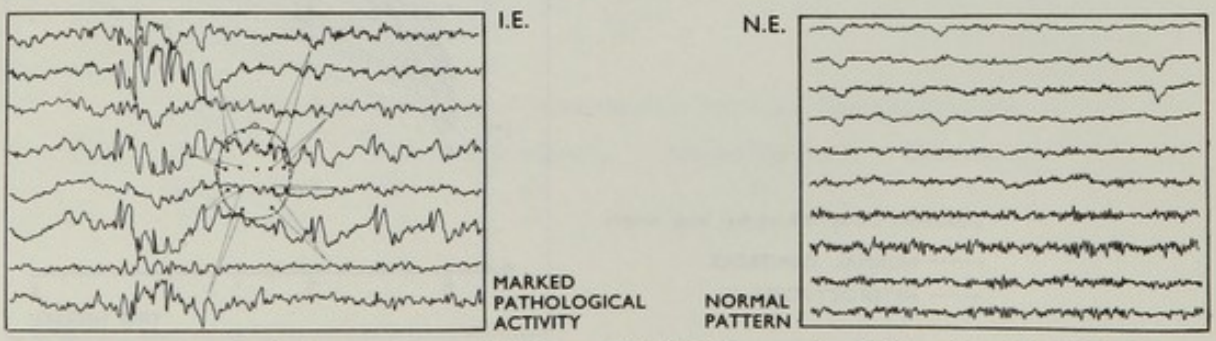
Examination of I.E. demonstrated a marked mental retardation, his physical development corresponding to the 25th percentile. Bone age was normal. He had blond hair and brown eyes. He could not stand by himself and made constant movements with his fingers. His tendon reflexes were hyperactive. The ferric chloride test of his urine was positive. The concentration of phenylalanine in the blood was 20 mg. percent and 30 mg./24 hr. were excreted in the urine. In the summer of 1959, at the age of 3½ years, the boy suffered for the first time from generalized convulsions. Since then his EEG (see below) has shown marked pathologic activity.

Forty-three family members residing in Israel have been repeatedly tested and three of these have been found to be also affected with phenylketonuria: (1) S.S.: a 28-year-old mentally retarded aunt of the propositus. Tendon reflexes were hyperactive. Phenylalanine concentration in blood was 25 mg. percent; excretion in the urine, 220 mg./24 hr. The EEG showed a slightly pathologic, nonspecific pattern. Estimated I.Q.: 35-40. (2) A.S.: a 32-year-old uncle of the propositus, of normal appearance, without clinical pathologic findings, employed as laborer in a factory. Hair color was brown. Phenylalanine concentration in serum: 16.5 mg. percent and urinary excretion 47 mg./24 hr. EEG showed a slightly abnormal pattern. Estimated I.Q. was 80. (3) N.E.: a 10-year-old cousin of the propositus. Her hair was blond and her tendon reflexes were hyperactive. Serum phenylalanine concentration was 25 mg. percent and the urinary excretion 35 mg./24 hr. The EEG (below) was normal. She had great difficulties in learning and attended a special class.

The family history indicates that a sister of the common grandmother of the parents had been affected by the same disorder. She had never married and had suffered from convulsions.

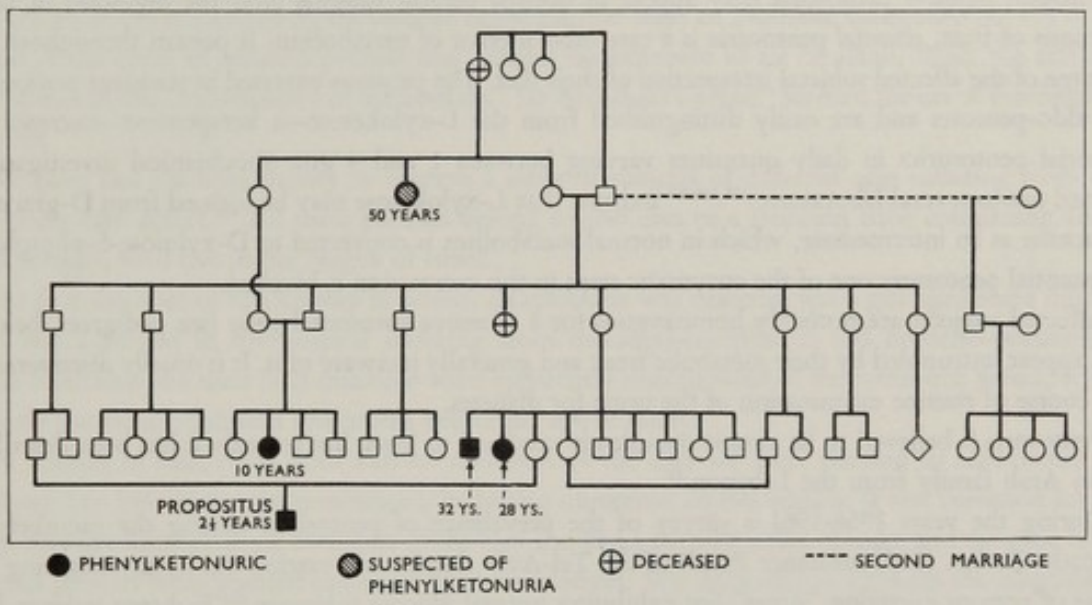
Apart from the community of Baghdad, we have diagnosed phenylketonuria in a Jewish family from Morocco, and other investigators (see p. 296) have found it in Jews from Yemen, Persia, and Afghanistan. *

ELECTROENCEPHALOGRAMS

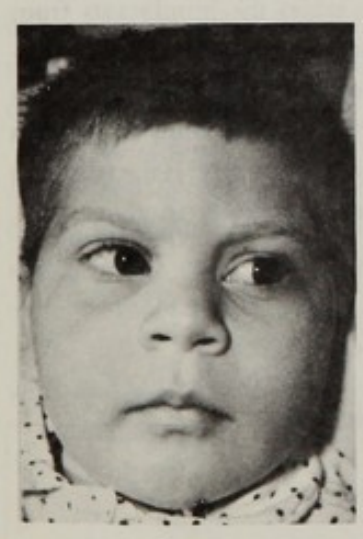


* The authors wish to thank Mrs. Kay Norton of the Dept. of Medical Photography, Beilinson Hospital, for her help.

PEDIGREE OF AFFECTED FAMILY



I.E.

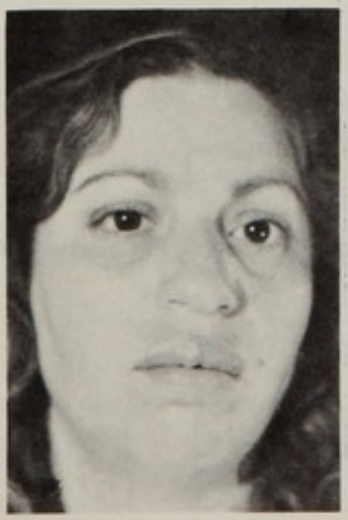


MALE, 2½ YEARS
EEG ABNORMAL
I.Q. 50

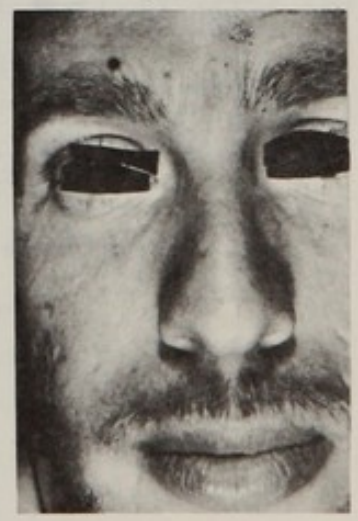
N.E.

FEMALE, 10 YEARS
EEG NORMAL
I.Q. 65

S.S.



FEMALE, 28 YEARS
EEG ABNORMAL
I.Q. 50



MALE, 32 YEARS
EEG ABNORMAL
I.Q. 80

Z. Laron, Z. Yonis, B. Bornstein
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Petah-Tiqva, Israel

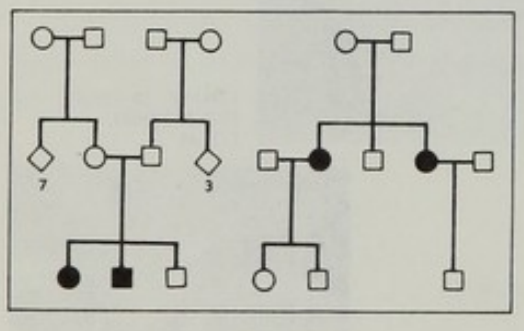
ALTHOUGH *transient* pentosuria may appear in normal human subjects after the ingestion of large amounts of fruit, *essential* pentosuria is a rare inborn error of metabolism. It persists throughout the lifetime of the affected subjects irrespective of their diet. The pentoses excreted in transient pentosuria are aldo-pentoses and are easily distinguished from the L-xyloketose--a ketapentose—excreted by essential pentosurics in daily quantities varying between 1 and 4 gm. Biochemical investigations carried out in several laboratories[125, 249-251] indicate that L-xyloketose may be formed from D-glucuronolactone as an intermediate, which in normal metabolism is converted to D-xylulose-5-phosphate. In essential pentosuria one of the enzymatic steps in this conversion is blocked.

Affected subjects are probably homozygous for a recessive autosomal gene (see pedigrees, below) and appear untroubled by their metabolic freak and generally unaware of it. It is usually discovered in the course of routine examination of the urine for diabetes.

Pentosuria is believed to be almost completely confined to Jews, but recently it has been described in an Arab family from the Lebanon.[27]

During the years 1956-1961 a survey of the prevalence of pentosuria among the members of Kupath-Cholim (Sick Insurance Fund) of the Tel-Aviv district was carried out by investigating the urine of persons excreting "sugar" but exhibiting normal glucose tolerance.[217] Eighteen independent cases (8 males and 10 females) were established in this population averaging 180,000 members during the period of investigation.

Among the affected subjects, all of whom were Ashkenazim (see table) the immigrants from various central European countries were represented in similar proportions as in the general population of Israel. Since the Ashkenazic group constitutes about 50 percent of all Kupath-Cholim members, we conclude that the prevalence of pentosuria is about 1/5000 Ashkenazim, or 10 times larger than estimated by Larson[153] for members of the New York Insurance Company. If the gene was homogeneously distributed among Ashkenazic Jews, its frequency would amount to about 1/70, which is close to the estimate given by Lasker and associates.[154]



REPRESENTATIVE PEDIGREES

KUPAT HOLIM SERIES

■ ● PENTOSURIA

DISTRIBUTION OF 36 PARENTS OF PENTOSURICS ACCORDING TO COUNTRY OF ORIGIN

Ashkenazim	*No. of parents*
Poland	18
Russia	8
Romania	8
Czechoslovakia	2
Other Communities	—

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Kupath-Cholim
Tel-Aviv, Israel

H. Hendel B. J. Ben-Assa

ALKAPTONURIA is the failure to metabolize homogentisic acid, an aromatic compound which is excreted in the urine of affected persons and darkens on exposure to air or alkali. With the accurate description of this "inborn error of metabolism" Sir Archibald Garrod[98] forecast the era of biochemical genetics.

We have had the opportunity to observe a series of subjects of different ages suffering from this extremely rare defect.[124] All these patients belong to one clan of a Bedouin tribe comprising about 1500 persons, who live in the Negev of Israel.

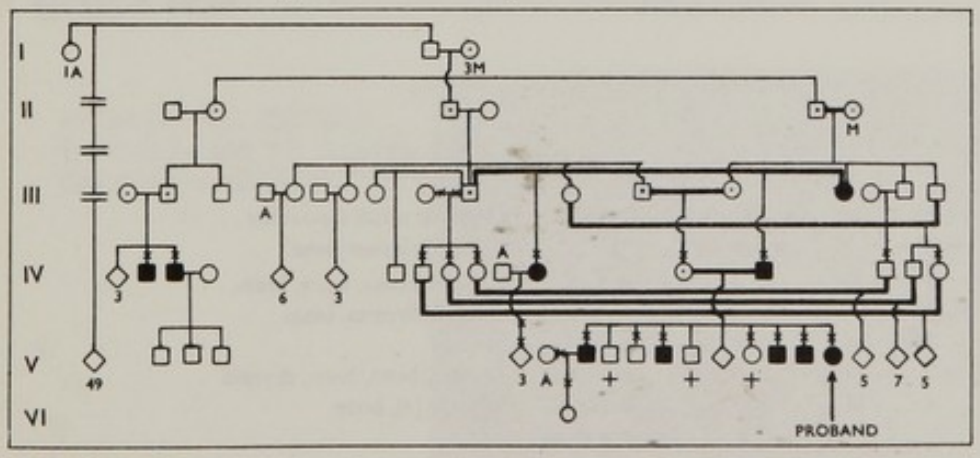
The first member of this kinship in whom alkaptonuria was detected was a girl aged three months who was admitted to the hospital suffering from meningo-encephalitis and broncho-pneumonia. These infections and their fatal outcome were apparently unconnected to the metabolic defect, which is rarely the cause of clinical symptoms before the age of thirty.

By a series of interviews with various members of the clan we were enabled to reconstruct the pedigree (see below) for six generations, including numerous cousin unions. It was common knowledge that the urine of some members of the clan showed a peculiar color change, and the nine living affected persons were pointed out to us by their relatives. We were able to confirm the diagnosis in each case by the examination of the urine, and we have also checked the urine of 14 unaffected members.

Three affected persons, who were over 30 years of age, suffered from various clinical symptoms indicated in the table (below). Although ochronosis and osteoarthritis have often been reported in such patients, the finding of urolithiasis in two of the present cases is of especial interest. The stones expelled by one affected male proved on examination to be composed of homogentisate derivatives.

This defect is generally ascribed to a recessive autosomal gene, and some of the more recent reports of dominant inheritance[172] have later been disclaimed.[173] The present pedigree furnishes a most interesting instance of the appearance of this trait in consecutive generations, without necessitating the assumption of its dominant transmission. We have indicated all the relatives of affected persons who were probably carriers and may have inherited the recessive gene from 3M in generation I.

The mother (III_1) of two affected males in generation IV is also assumed to be a carrier although we were unable to trace any blood relationship between her and the main branch of the family tree.



PEDIGREE OF AFFECTED FAMILY

● ■ ALKAPTONURIC
⊙ ⊡ PRESUMED CARRIER
A DESCENDANT OF I-1A
M RELATED TO I-3M
\+ DIED IN INFANCY
× TESTED BY OTHERS
—— FIRST COUSIN MARRIAGE

COMPLICATIONS IN THREE HOMOZYGOTES

Case	*Sex*	*Age, in years*	*Ochronosis*	*Osteoarthritis*	*Urinary calculi*
IV 8	female	over 60	—	+	—
IV 10	male	58	+	+	+
IV 2	male	over 30	+	—	+

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Tserifin, Israel

SOME 60 CASES of primary oxalosis, a rare inborn error of metabolism, have been described in the medical literature.[20, 168, 214, 219, 265] This disease mainly affects children and is characterized by increased urinary excretion of oxalates and progressive renal failure. At autopsy calcium oxalate crystals are found in the kidneys and other organs. The disease has been reported in siblings as well as in other members of the same family. Consanguinity has been noted in few cases. Complete genetic studies of such families indicated that the inheritance was recessive in some cases[20, 214] and dominant in others.[168, 219]

During the last few years 4 cases of oxalosis have been studied in this hospital.[139, 211] Three of them were diagnosed at autopsy, and one during life. The children were between the ages of 3 and 19 months; three were boys and one a girl. All 4 children belong to one large kinship of Tripolitanian Jews living now in Israel (see pedigree). Consanguineous marriages are common in this group.

The diagnosis of oxalosis in the propositus, a boy aged 5 months, led to the investigation of the family and to the ascertainment of three additional affected children. In the pedigree these patients are numbered according to the order of their births. The parents of the affected children 2 and 3 are second cousins once removed and are, moreover, related through the two brothers of generation I. The mother of patients 1 and 4 is a paternal aunt of patients 2 and 3. We were unable to trace any blood relationship between her and her husband, but its existence cannot be excluded with confidence.

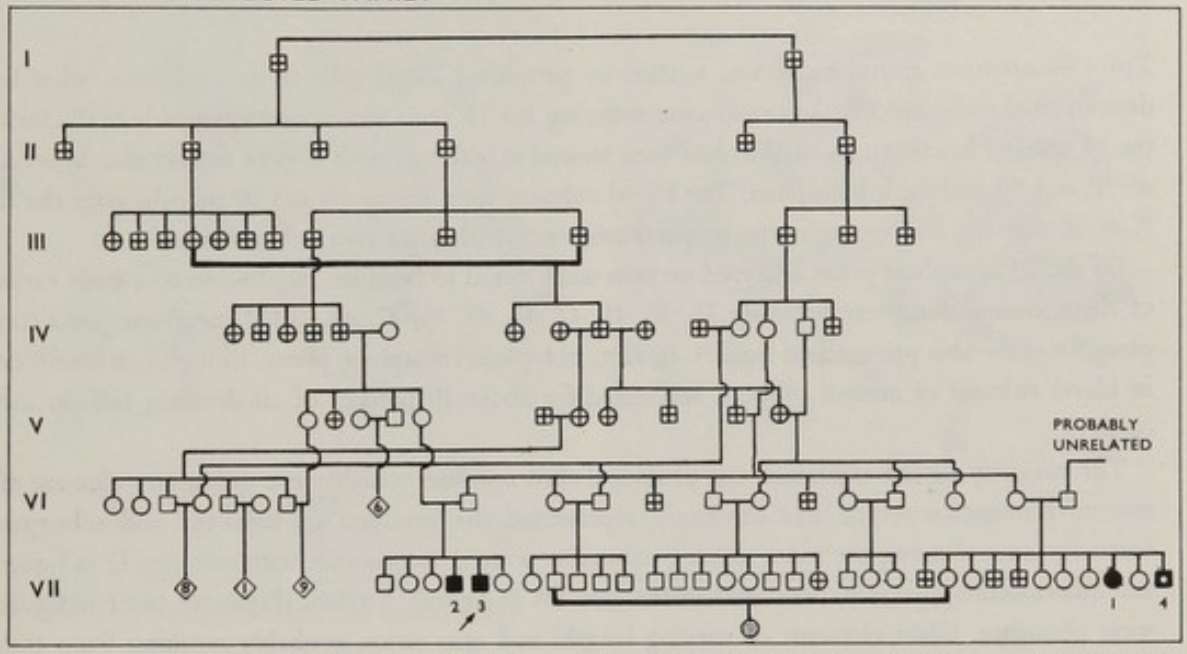
At autopsy large amounts of calcium oxalate crystals were found in the kidneys (see figure), and lesser amounts or single crystals in bones (see figure), heart muscle, thyroid, brain, thymus, and lungs. Patient 4 was hospitalized at the age of 2½ months because of continuous vomiting and failure to thrive. Clinically the main findings were uremia with acidosis and increased urinary secretion of calcium oxalate. A biopsy taken from the iliac crest showed an accumulation of calcium oxalate crystals at the epiphyseal border and in the adjacent bone marrow.

The biochemical error in the present family may be due to a dominant gene with variable penetrance and expressivity but it appears more likely that we are dealing with a recessive character. In an inbred community consanguinity among the parents of affected individuals is not a reliable criterion of recessive inheritance. Nevertheless, this mode of inheritance appears indicated in our kinship by the clinically healthy condition of the four parents to whom affected children were born. Urine examination for oxalates of the relatives of these infants is in progress in order to determine whether this defect, like many other recessive traits, has some slight expression in the heterozygote.

SUMMARY OF FINDINGS IN FOUR AFFECTED CHILDREN

Case number	*Sex*	*Age at diagnosis, in months*	*Diagnosis*	*Organs in which Ca-oxalate crystals were found*
1	F	3	at P.M.	kidneys, bones, heart, brain, thyroid, thymus, lungs
2	M	18	at P.M.	kidneys
3	M	5	at P.M.	kidneys, bone, heart, thyroid
4	M	9	Biopsy of crista iliaca	kidneys (?), bone

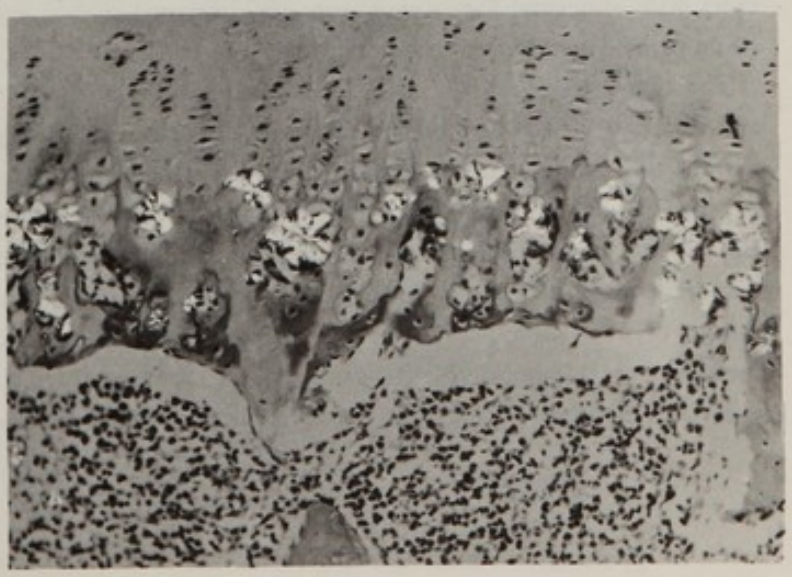
PEDIGREE OF AFFECTED FAMILY



MACROSCOPIC SECTION OF KIDNEY

MASSIVE ACCUMULATION OF CRYSTALS (× 4)

MICROSCOPIC SECTION THROUGH RIB AT COSTO-CHONDRAL SECTION



PHOTOGRAPHED IN PARTLY POLARIZED LIGHT. (× 100) STAIN E.H. NOTE OXALATE CRYSTALS

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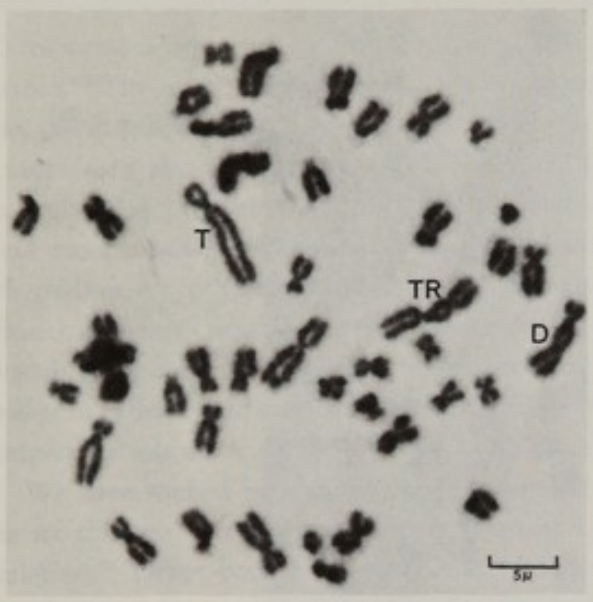
THE CHROMOSOME complement was studied in peripheral blood cells from a woman who had developed chronic myeloid leukemia after suffering for 11 years from polycythemia vera.[253] During the 14 years of her illness the patient had been treated at intervals with X rays, intravenous injections of ^{32}P and ^{131}I and with busulphan. The blood cultures were set up 15 and 20 months after the last X-ray treatment, and chromosome preparations were made after two or three days.

Of the 70 metaphase plates analyzed no two were found to be alike. In addition to a wide variety of chromosome numbers, including 35, 36, 41, 42, 43, 45, 46, 47, 48, and 49, near-tetraploid complements were also present (see figure). In fact, polyploid metaphase plates, though extremely rare in blood cultures of normal subjects, accounted for about 10 percent of all dividing cells in these cultures.

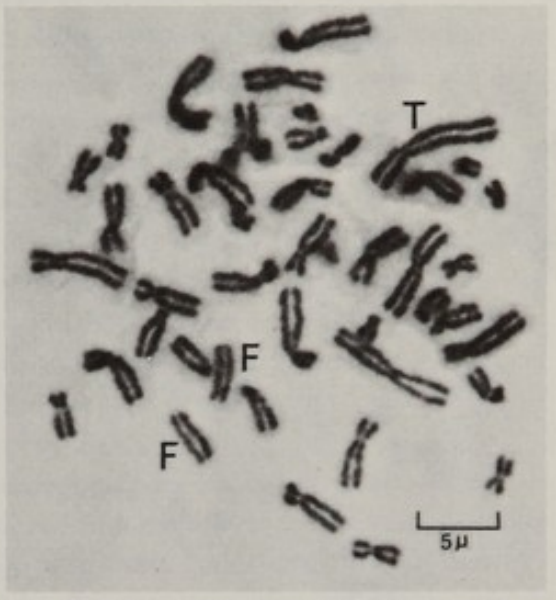
The majority of cells contained one or several chromosomes which were unlike any element of a normal human karyotype and obviously represented the products of breakage and subsequent rearrangement. Among the more striking anomalies were chromosomes with two (see D in figures) and others with apparently three centromeres (see TR in figure). Acentric fragments (see F in figures) were abundant. Giant elements of varying lengths and arm ratios, probably resulting from translocations, were present in many cells (see T in figures). Five chromatid breaks were identified among 70 cells.

Occasional deviations from the normal karyotype have been described in several cases of acute leukemia.[129, 212, 247] A few of these subjects displayed a uniform change in all their affected cells, whereas several different chromosome complements were seen in the majority. In contrast, many patients suffering from chronic myeloid leukemia exhibit a consistent change in all affected cells[185, 247]—namely, the presence of the minute Philadelphia chromosome, usually ascribed to a deletion in one of the four small acrocentrics. In most of these cases it is difficult to establish the nature of the relationship between the leukemia and the chromosomal deviations in view of the various treatments to which these patients had been exposed prior to the chromosome analysis. Chemotherapeutic agents, radioactive compounds, and in particular X rays are liable to induce chromosome aberrations which may persist in the hematopoietic tissues.[30, 40, 247] However, such induced chromosome changes are probably subject to progressive elimination after the cessation of the treatment.[40] Moreover, leukocytes with abnormal karyotypes were also observed in leukemic patients given no treatment that could be held responsible for the chromosome breakage.[212]

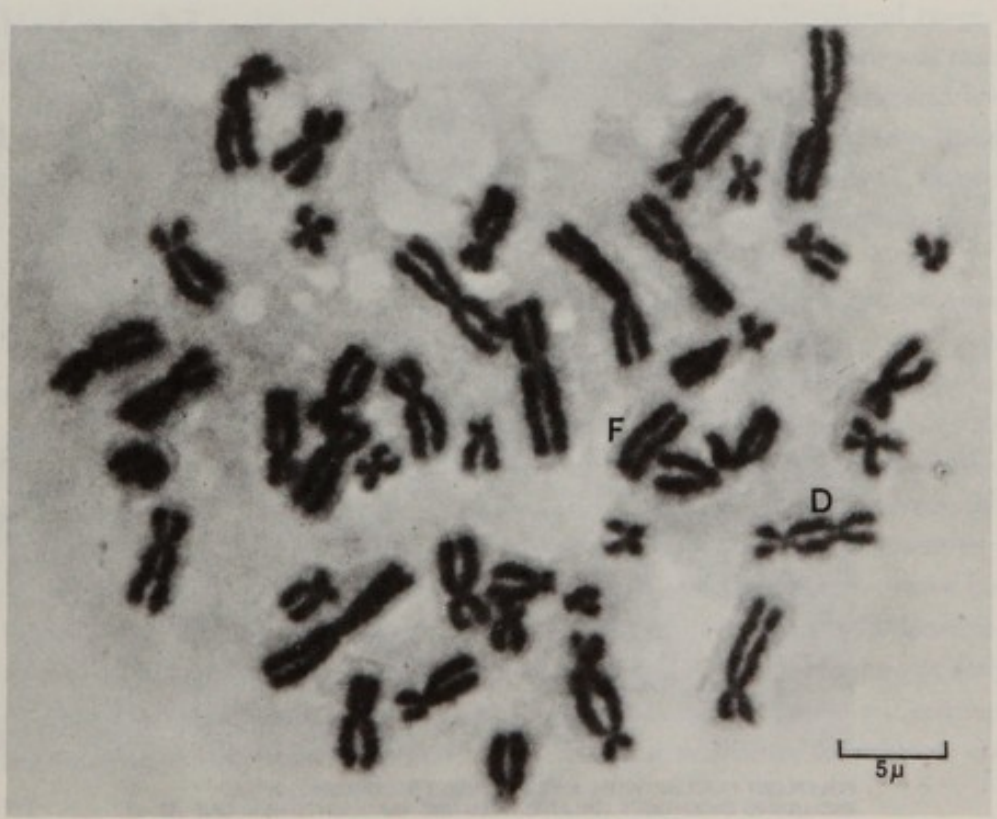
The case described here differs from many others of chronic myeloid leukemia in the intensity and variety of damage to the chromosomes. It is possible that this damage may in part be due to the various therapeutic agents received by this patient during her prolonged illness. Nevertheless, we hesitate to ascribe this comprehensive injury to extraneous agents alone. When 15 months had elapsed after the last irradiation, the changes were abundant. Even 5 months later their frequency had not declined. Some of the chromosome types observed are hardly expected to survive a series of mitotic cycles. This applies to the acentric fragments and in particular to the chromatid breaks. For these reasons, intraneous chromosome damage causally related to the leukemia should be considered as a possible source of an endless variety of deviant cells in this patient.



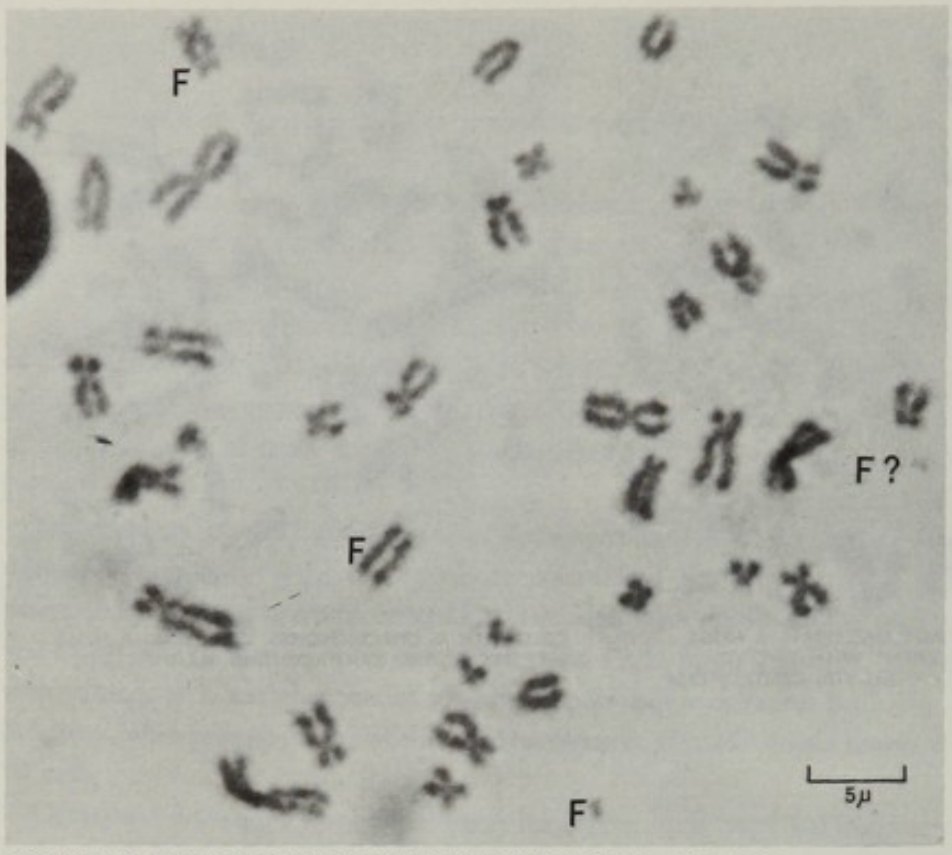
CELL WITH 44 CHROMOSOMES, INCLUDING A HUGE CHROMOSOME (T). ONE ELEMENT WITH TWO (D) AND ONE WITH PROBABLY THREE (TR) CENTROMERES



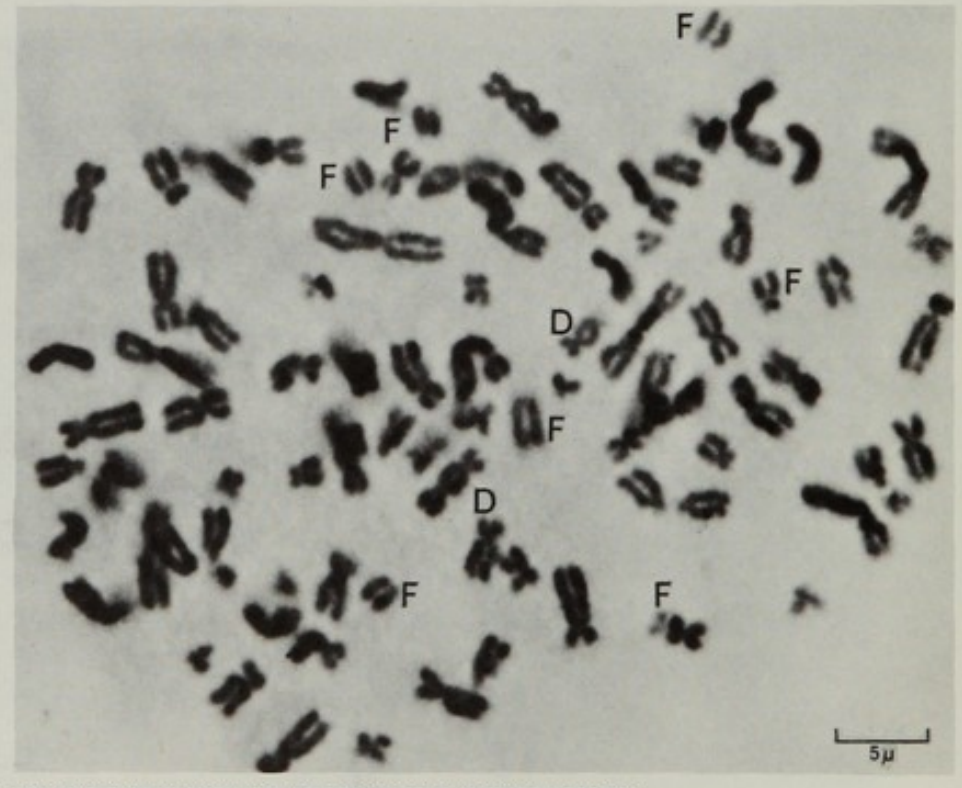
CELL WITH 45 CHROMOSOMES, INCLUDING A HUGE ELEMENT (T) AND TWO ACENTRIC FRAGMENTS (F)



CELL WITH 45 CHROMOSOMES, INCLUDING ONE DICENTRIC (D) AND ONE ACENTRIC ELEMENT (F)



CELL WITH 36 OR 37 CHROMOSOMES, INCLUDING SEVERAL SMALL AND LARGE ACENTRIC FRAGMENTS (F). NOTE THE PROXIMITY OF THE UPPER FRAGMENT TO A SMALL METACENTRIC CHROMOSOME.



POLYPLOID NUCLEUS WITH APPROXIMATELY 95 CHROMOSOMES. INCLUDING DICENTRICS (D); AND ACENTRIC FRAGMENTS (F) — ONE AT LOWER RIGHT IN CLOSE ASSOCIATION WITH A SMALL METACENTRIC.

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J. Chowers J. W. Czaczkes E. N. Ehrenfeld

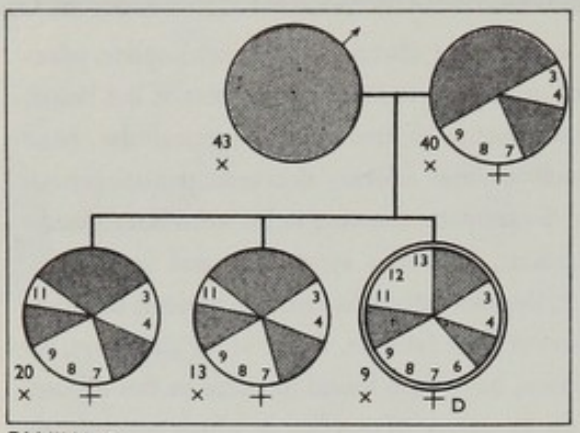
OSTEOGENESIS IMPERFECTA is commonly regarded as a dominant character with incomplete penetrance.[215] The most striking feature is the occurrence of multiple spontaneous fractures of the bones, but the inability to produce one or more of the components of the normal intracellular bone matrix may also manifest itself in other features, such as blue sclerae, deafness, dentinogenesis imperfecta, and hypermotility of the joints. Because of the frequent association between bone disease and renal tubular dysfunction, as in osteomalacia, rickets, Fanconi's syndrome, and hyperparathyroidism, we considered it worth while to search for analogous metabolic errors in patients suffering from osteogenesis imperfecta and in the healthy members of their families. As far as we are aware, no metabolic disorders, other than connective tissue dysplasias, have been found to occur in this disease, either in patients or in members of their families, with the exception of one case in which osteogenesis imperfecta was accompanied by mental retardation and cystinosis.[35]

We have studied by two-dimensional paper chromatography the pattern of urinary excretions in six children suffering from osteogenesis imperfecta and in a number of their clinically healthy relatives.[58] Other bone diseases clinically resembling osteogenesis imperfecta, such as Fanconi's syndrome, rickets, and hyperparathyroidism, were ruled out by adequate studies. Pathologic amounts of amino acids were observed in the urine of all patients, except one who suffered from severe chronic urinary infection. The general pattern was similar to that found in Fanconi's syndrome. The majority of the patients' relatives showed a similar pattern of amino acid excretion. The urine of the unaffected relatives frequently contained fewer types of amino acids and smaller quantities of each type than that of the patients. In no case did any of the members of the family excrete an amino acid which was not present in the patients' urine. The amino acids excreted by members of all three families are shown in the pedigrees (overleaf). Blood amino acid concentrations were all within normal range, both in the patients and in their families.

The blood creatinine level in the six patients tested were all below the normal range, whereas most of their relatives had normal blood creatinine levels. The creatinine clearance was examined in several patients and appeared to be elevated (see diagram, overleaf). Blood uric acid levels were normal in all members of the first family. In the other two families, the five patients had definitely low values, and several of their relatives also tended to have low values. In family C., three out of six healthy members had values under 3.5 mg. percent; in family Ch., five out of seven healthy members had similarly low values.

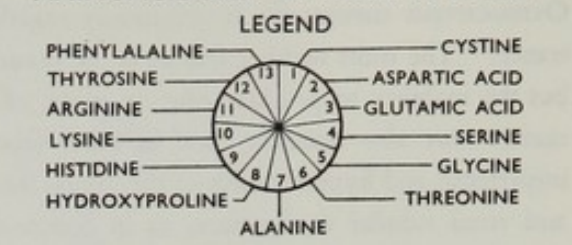
Our observations appear to indicate that a renal tubular dysfunction may be associated with osteogenesis imperfecta, as in Fanconi's syndrome, rickets, and hyperparathyroidism. It is possible that there exists some common underlying factor, such as an identical enzyme system, responsible both for the formation of the bone substance and for the transfer mechanism in the renal tubules.

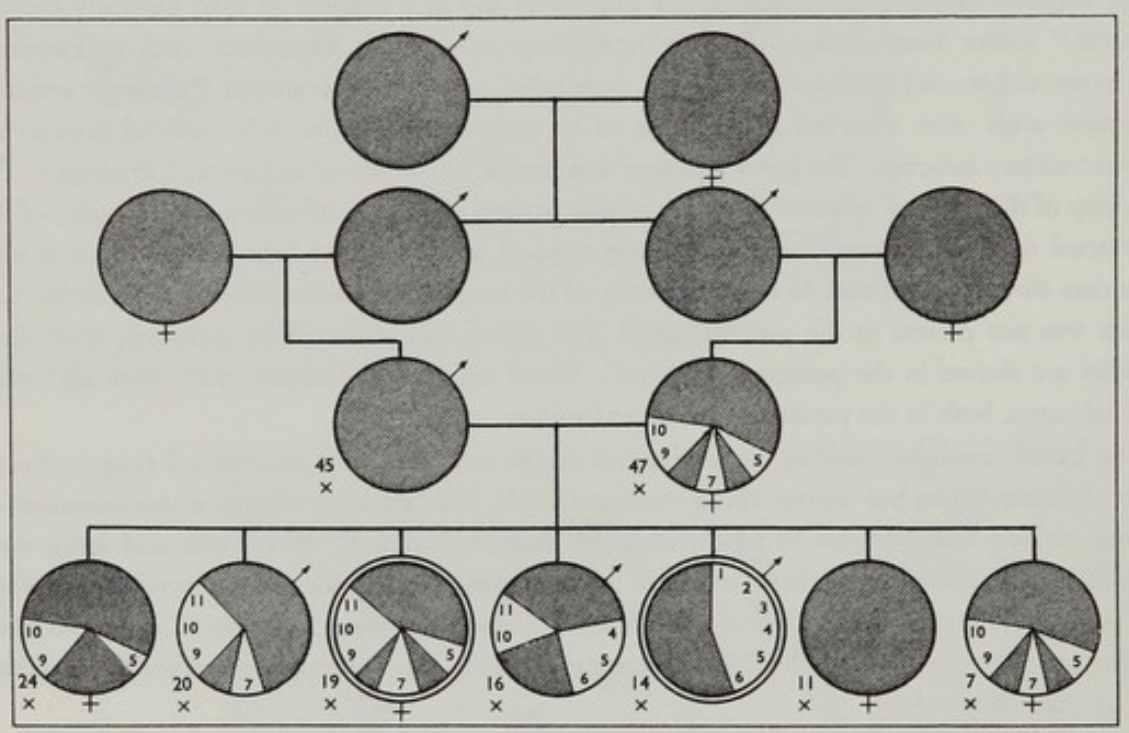
The genetic interpretation of the pedigrees presented poses several problems. Bone fragility in our families appears to follow the usual pattern of dominance with incomplete penetrance. We should therefore expect to find abnormal amino acid excretion in the affected subjects and in a certain proportion of their relatives who may be assumed to carry the abnormal gene without manifesting bone fragility. However, in each of these families the number of persons with abnormal amino acid excretions exceeds the expected on the hypothesis of simple dominance. In two of the pedigrees abnormal segregation ratios could possibly be due to consanguinity. The amino acid secretion should be studied in a larger series of families affected with osteogenesis imperfecta before conclusions are drawn.



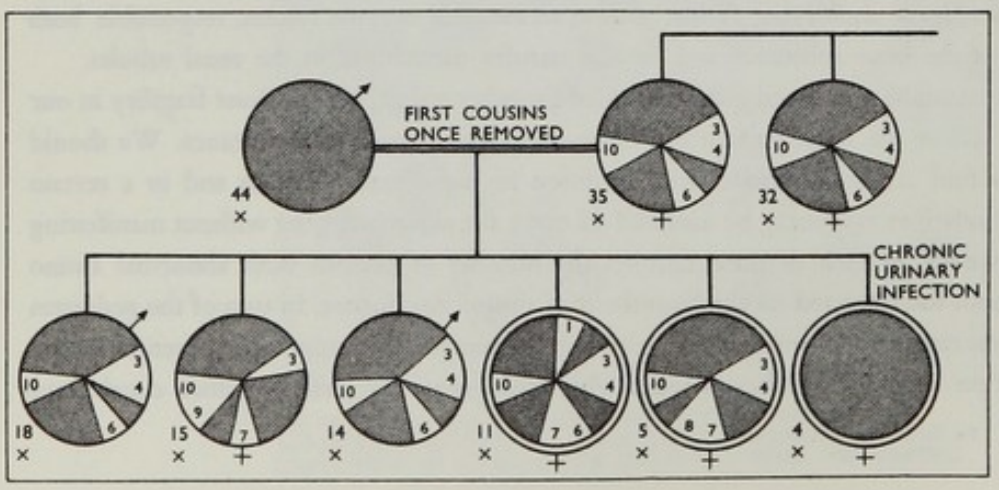
FAMILY K
ORIGIN: GERMANY

AMINOACIDURIA IN THREE FAMILIES





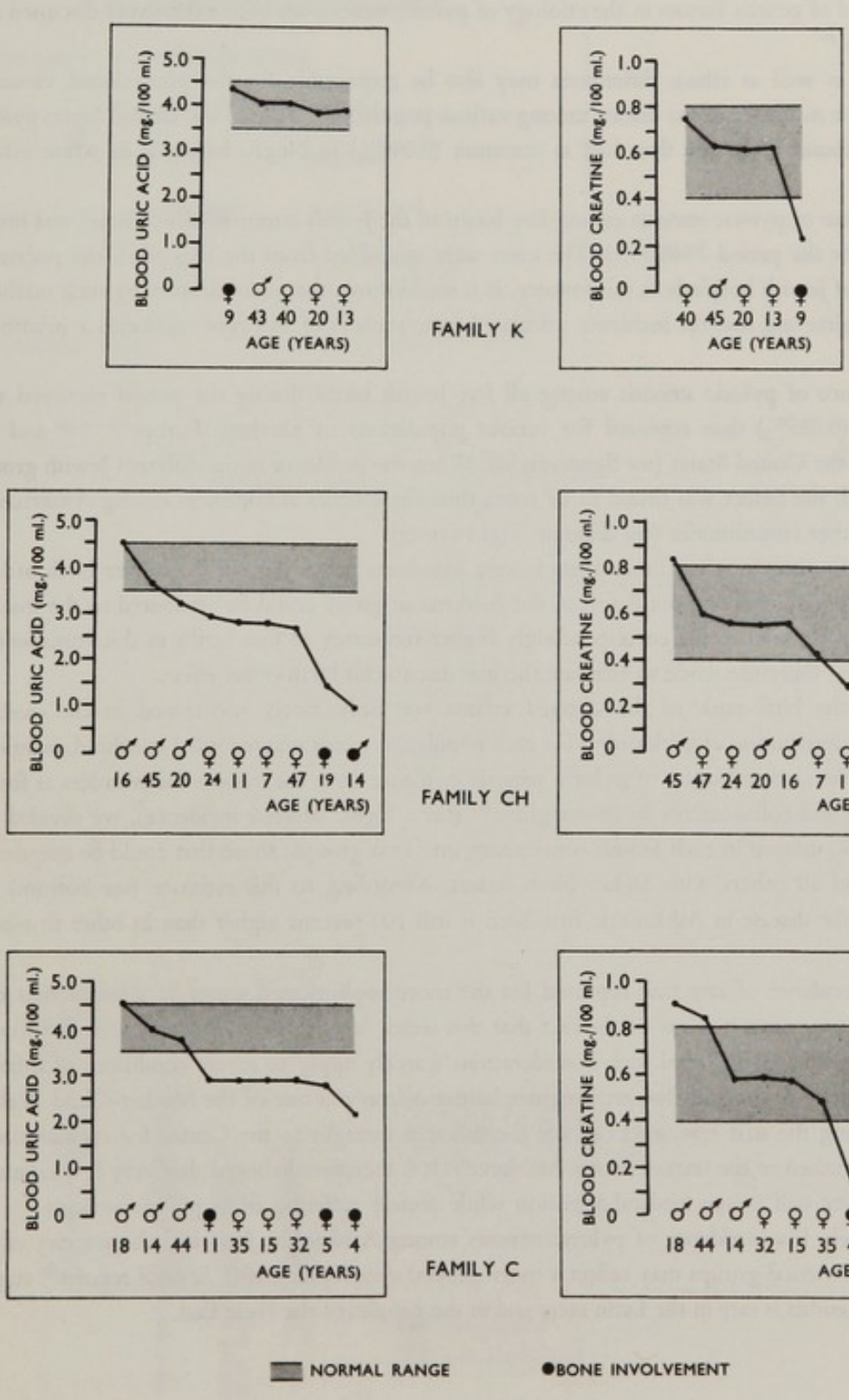
FAMILY CH.
ORIGIN: YEMEN



FAMILY C
ORIGIN: IRAQ

BLOOD URIC ACID BLOOD CREATINE

IN THREE FAMILIES AFFECTED WITH OSTEOGENESIS IMPERFECTA



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INFANTILE PYLORIC STENOSIS is an abnormality characterized by hypertrophy of the pyloric musculature resulting in a tumor mass which constricts the lumen of the pyloric canal and impedes gastric emptying. The pyloric constriction can be demonstrated by roentgenographic examination after ingestion of barium; the constricted canal appears like a "rat tail." The relative importance of environmental and of genetic factors in the etiology of pyloric stenosis has been extensively discussed in a recent review.[51]

Ecological as well as ethnic differences may also be responsible for the pronounced variation observed in the incidence of the disease among various populations. Thus in the United States pyloric stenosis was found to be less than half as common (0.046%) in Negro babies as in white infants (0.12%).[151]

The incidence of pyloric stenosis among live births of the Jewish communities of Israel was investigated[149, 150] for the period 1948-1953. The cases were assembled from the files of all the pediatrics departments of Jewish hospitals in the country. It is well known that identification by such methods is rarely complete and that the incidence calculated from surveys of this type represents a minimum estimate.

The incidence of pyloric stenosis among all live Jewish births during the period surveyed was much lower (0.055%) than reported for various populations of northern Europe[155, 166, 256] and for Caucasians in the United States (see figure, right). When the incidence in the different Jewish groups was calculated, the defect was found to be more than three times as common among Ashkenazim as in all the other communities (see diagram, right center).

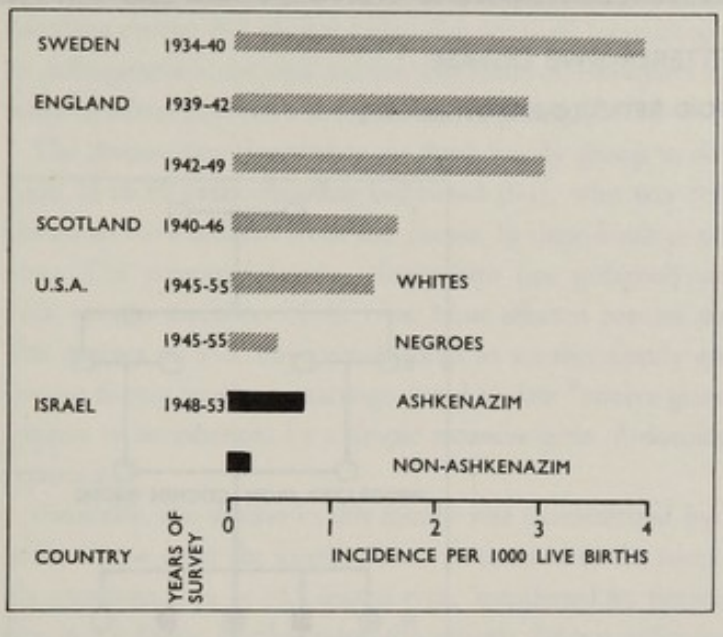
Since pyloric stenosis occurs more often among first-born babies than in the higher birth orders, the relative preponderance of the defect in the Ashkenazic group could be attributed to the smaller average sibship size and to the correspondingly higher frequency of first births in this community. An attempt was therefore made to estimate the bias due to this birth-order effect.

Although the birth-rank of the affected infants was only rarely mentioned in the medical files, the total distribution of birth orders for each population sector was recorded in official statistics.[13] Assuming a *relative* distribution of pyloric stenosis incidence over the various birth orders as found by McKeown and collaborators in Birmingham[165] (for a higher *absolute* incidence), we divided the cases of pyloric stenosis in each Jewish community into two groups: those that could be assigned to first births and all others with higher birth orders. According to this estimate (see bottom) the frequency of the disease in Ashkenazic first-born is still 100 percent higher than in other first-born babies.

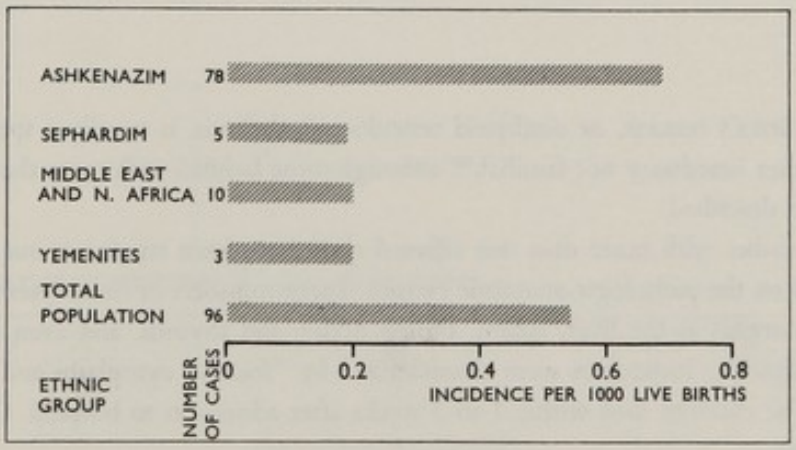
A higher incidence of any trait reported for the more sophisticated sector of a population may be regarded as spurious in view of the fact that this sector has better access to medical facilities. It should be stressed that in Israel such considerations scarcely apply to severe conditions of infancy. The vast majority of pregnant women register before delivery at one of the Mother-Child Welfare Centers. During the first few weeks of life the infant is brought to the Center for regular check-ups, and it is rushed to the station in any emergency. It is therefore believed that very few infants of any community will escape medical attention while acutely suffering from pyloric stenosis.

The relatively low incidence of pyloric stenosis among Ashkenazic Jews and the scarcity of this defect in the Oriental groups may reflect a more general geographic trend. Several reports[256] suggest that pyloric stenosis is rare in the Latin races and in the peoples of the Near East.

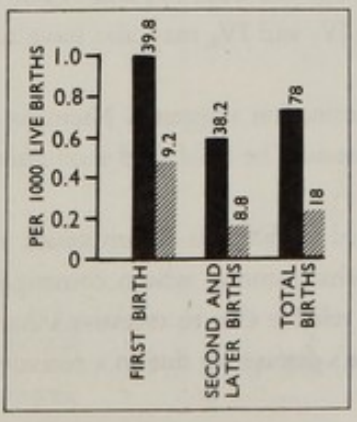
INCIDENCE OF PYLORIC STENOSIS IN DIFFERENT COUNTRIES



INCIDENCE IN DIFFERENT ETHNIC GROUPS IN ISRAEL 1948-53



ESTIMATED DISTRIBUTION AMONG FIRST AND LATER BIRTHS



THIS ESTIMATE IS BASED ON THE ASSUMPTION THAT THE BIRTH RANK DISTRIBUTION AMONG AFFECTED INDIVIDUALS IN ISRAEL IS SIMILAR TO THAT OF BIRMINGHAM[165]

ASHKENAZIM
NON-ASHKENAZIM

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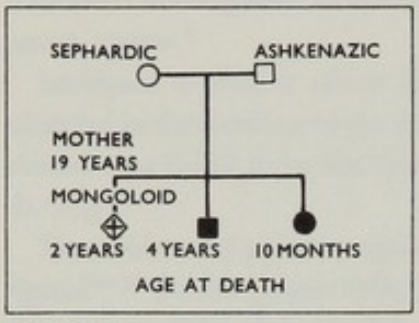
Jerusalem, Israel

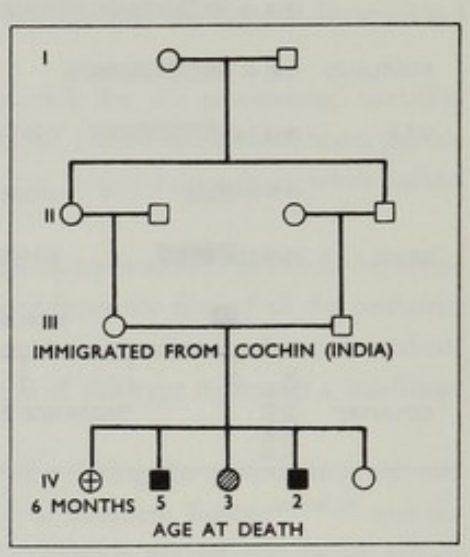
LETTERER-SIWE DISEASE

(NON-LIPOID RETICULO-ENDOTHELIOSIS)



FAMILY A

⊕ ⊕ DIED : UNKNOWN CAUSE
■ DIED : LETTERER-SIWE
▨ DIED : CAUSE "NOT NIEMANN PICK"



FAMILY B

Letterer-Siwe's disease, or nonlipoid reticulo-endotheliosis, is usually a sporadic disease. It is said to be neither hereditary nor familial,[224] although some families with more than one affected member have been described.

Two families with more than one affected child have been treated at our clinic.[84] The diagnosis was based on the pathologic-anatomic picture. Large numbers of histiocytes were observed infiltrating such organs as the liver, spleen, lymph nodes, and thymus, and even replacing their tissues. The proliferating histiocytes were characterized by "foamy" cytoplasm and storage of lipoid substances. The children died within 1 to 3 weeks after admission to hospital. Only one was over one year of age.

In family A the two affected children—a boy of 4 years and a girl of 10 months—died within the same week and had been in direct contact before their brief hospitalization. In family B any contact between the affected infants is excluded since all died during the first months of life. In this family one must consider the possibility that in addition to the two boys IV_2 and IV_4 in whom Letterer-Siwe's disease was diagnosed, one or both of the girls IV_3 and IV_1 may also have suffered from the same condition.

The infant IV_3 was admitted to hospital, where clinical examination suggested Niemann-Pick's disease, though the laboratory tests could not confirm this diagnosis. The child died soon afterwards without the cause of death being established.

Whereas in family A the parents were unrelated and belonged to different communities, the parents in family B were first cousins and immigrants from Cochin, among whom consanguineous marriages are so common (see also p. 353) that they furnish no reliable clue to recessive inheritance.

The possibility that at least some of the cases of Letterer-Siwe's disease are due to a recessive gene must be kept in mind.

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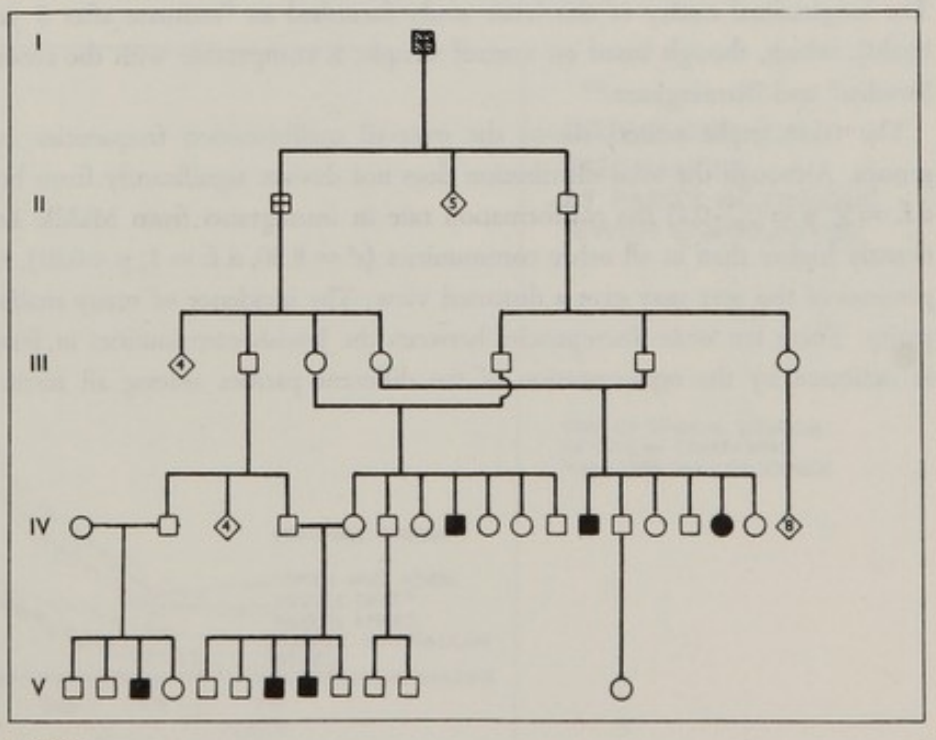
S. L. Weissman C. Khermosh A. Adam

ARTHROGRYPOSIS IS A clinical entity characterized by multiple congenital contractures of the joints.[128] Its pathogenesis is not well understood. Some of the reports in the literature deny familial occurrence, whereas others describe a definite familial pattern.[95, 126, 234]

The disease was observed in an Arab family group in six individuals of both sexes and of ages from 2½ to 20 years. Another individual (I-1), who was dead at the time of the survey, is also reported to have suffered from the disease. In these kinships consanguineous marriages are very common. The presented family relationships (see pedigree) were established by repeated interviews with various members of the clan. Most affected persons were related through both their parents. The mother of V-3, however, belongs to another family group, which is said to be related to the present family tree by a marriage stated to date "twelve generations back." In this family the disease appears to be inherited by a simple recessive gene. A dominant mode of transmission has also been reported.[234]

Clinically, the disease in this family was characterized by the flexion type of contractures either at the elbow or at the knees. This is in contrast to the more usual finding of contractures of either the extension type or of a mixed type, manifested by flexion in the upper extremity and by extension in the lower. Furthermore, the patients did not suffer from dislocation of the hip, though some had foot deformities such as equino-varus or equino-valgus. The condition is congenital and nonprogressive.

ARTHROGRYPOSIS IN AN ARAB FAMILY



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Government Hospital
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An estimate of the incidence of major malformations in the Jewish communities[170] was based on all live births that had occurred in the four maternity departments of the Jerusalem district during the period 1950-1959. The number of live births in these four maternity wards (Hadassah, Bikur-Cholim, Shaare Zedek, and Misgav Ladach) was 49,563 during this period, according to Dr. H. S. Halevi of the Ministry of Health. Since home deliveries during the same period amounted to less than 4 percent of all births,[19] the maternity ward sample may be considered representative of all communities and economic levels.

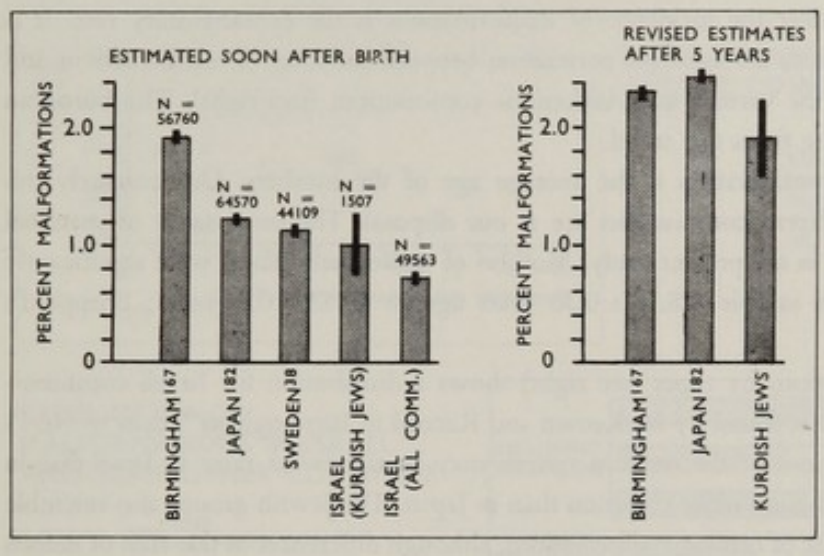
The case notes of these departments were carefully searched for all malformations noted in live-born babies during their stay in hospital (five days on the average for girls and up to eight days for boys). During this period the babies are given at least two medical examinations, one on the day following delivery and the second before discharge.

For the purpose of the present survey, malformations were defined as "gross deviations from normal anatomical structure." Many authors include in this category a series of defects which were excluded from the present compilation for a variety of reasons. Some (such as luxation of the hip) are rarely manifest at birth, some (such as hydrocoele and cryptorchidism) are often transitory in nature, and others (such as pulmonary atelectasis) cannot be accurately diagnosed except at autopsy but are frequently recorded by the practitioner without adequate pathological investigation.

The deliberate exclusion of malformed stillbirths from the present material precludes a strict comparison of our results with those of other surveys in which the malformation rate was determined for stillbirths and live births combined.[38, 167, 182] The recorded malformation rate in stillbirths[38] (with autopsy and without) suggest that inclusion of these cases would have raised the present estimate by 15 to 25 percent. On the other hand, the exceptionally high rate of hospital deliveries in Israel should make for more complete recording of defects in live births. These considerations may justify the attempt to compare the present estimate with those obtained by a variety of methods in other countries (see top right).

The information obtained in the general Jerusalem survey is supplemented by material collected by the Zoology Department in a study (see pp. 183, 344-349) devoted to the Kurdish community. The longitudinal outlay of this latter study furnished an "estimate after 5 years" (including stillbirths), which, though based on a small sample, is comparable with the corresponding figures for Sweden[38] and Birmingham.[167]

The table (right center) shows the over-all malformation frequencies in the various Jewish groups. Although the total distribution does not deviate significantly from homogeneity ($\chi^2 = 8.0$ d.f. $= 5$, $p = 0.2$-0.1) the malformation rate in immigrants from Middle East countries is significantly higher than in all other communities ($\chi^2 = 8.30$, d.f. $= 1$, $p < 0.01$). However, crude comparisons of this sort may give a distorted view. The incidence of many malformations varies with parity. There are wide discrepancies between the Jewish communities in fertility rates per couple as indicated by the representation of the different parities among all births (see bottom right).



MAJOR MALFORMATIONS

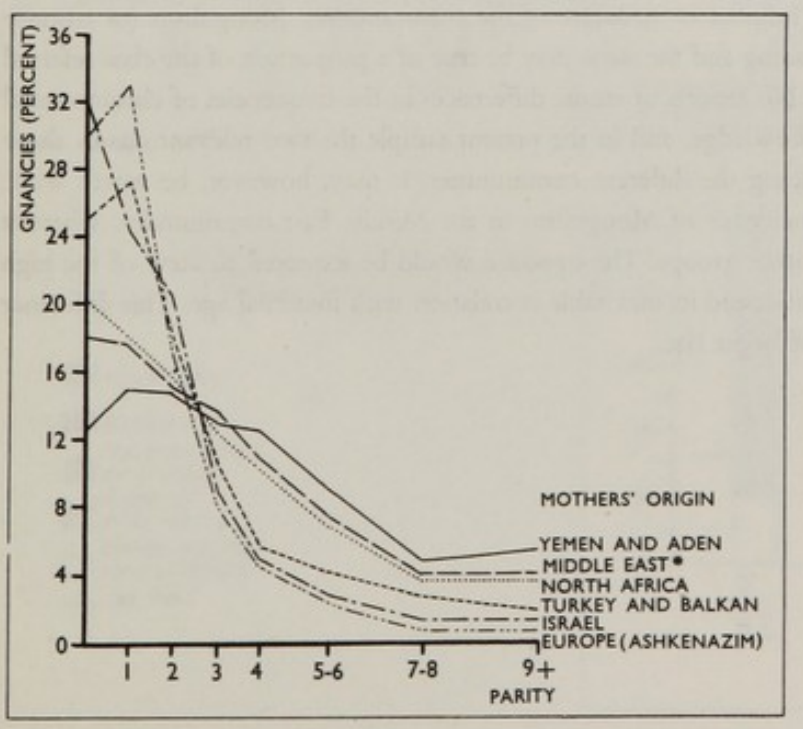
HEIGHTS OF BLACK BARS: ± 1 ST. E.

N = NUMBER BIRTHS

FREQUENCY OF MAJOR MALFORMATIONS IN VARIOUS ETHNIC GROUPS IN ISRAEL (1950-1959)

Mother's origin	*No. of malformations*	*No. of births*	*% malformations ± ST.E*
1. Middle East•	100	11,189	0.894 ± 0.089
2. Yemen and Aden	18	2,797	0.644 ± 0.151
3. India	3	215	1.395 ± 0.800
4. North Africa	56	8,320	0.673 ± 0.090
5. Turkey and Balkan	14	2,654	0.528 ± 0.141
6. Europe and U.S.A.	63	8,966	0.703 ± 0.088
7. Israel	89	14,991	0.594 ± 0.063
8. Other countries	8	431	1.856 ± 0.650
Total	351	49,563	0.709 ± 0.038

For homogeneity test, items 3, 7, and 8 were pooled.



DISTRIBUTION OF PREGNANCIES BY PARITY IN VARIOUS JEWISH COMMUNITIES

ONE OF SEVERAL SOURCES OF BIAS IN COMPARING MALFORMATION INCIDENCE

• Middle East: Baghdad, Kurdistan, Persia, Syria, and Lebanon.

Another factor which may affect the incidence of malformations is the consanguinity rate. It is therefore of some interest to note the apparent correlation between the rates of malformations and of first-cousin marriages[103] in the various non-Ashkenazic communities (top right). The European group is the only one diverging from this trend.

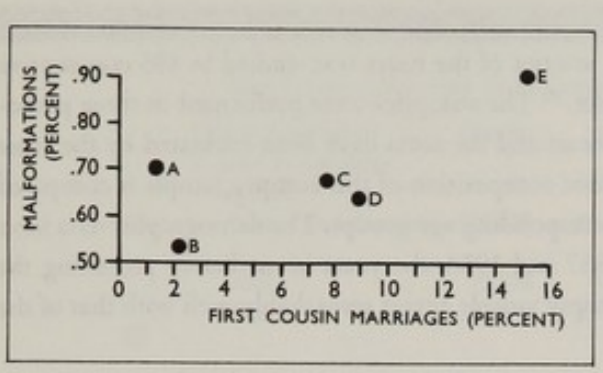
Another factor deserving consideration is the average age of the mothers. Unfortunately, no maternal age data for the different communities are at our disposal. The importance of maternal age[191] is confirmed once again in the present study. Mothers of malformed infants were significantly older than all mothers of the sample (28.18 ± 0.36 years against 27.13 ± 0.33 years; Sheppard's adjustment for grouping.)

A breakdown of malformations by types (see right) shows a distribution for Israeli communities which is more similar to that found by McKeown and Record in Birmingham[167] than to Neel's Japanese sample.[182] Malformations of the nervous system may be somewhat rarer in Israel than in the other Caucasian samples, though more common than in Japan. The Jewish groups also resemble the European samples in the rate of cardiac malformations, although differences in this class of defects may arise from lack of generally accepted criteria.

A breakdown of the Israel material by types of malformation and community (see right), despite the small size of the subsamples, shows that malformations of the central nervous system contribute significantly more to the total in immigrants from the Middle East countries than in the other communities ($\chi^2 = 13.1$, d.f. $= 1$, $p < 0.001$). The complete absence of this type of defect in the small sample of Sephardic Jews from the Balkan countries and Turkey also deserves attention.

The composition of the group classed as "other malformations" in the preceding diagram indicates some further differences among the communities. The various types of cleft lip and/or palate contribute significantly more to the total malformation rate in the Middle East communities than in the others ($\chi^2 = 7.8$, d.f. $= 1$, $p < 0.01$), whereas hypospadias may possibly occur more often in the Balkan group than in the others.

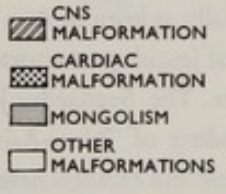
Recent advances in human cytology have focused attention on a group of malformations which are due to gross changes in the number or structure of the chromosomes. Mongolism (or trisomy 21 syndrome) falls under this heading and the same may be true of a proportion of the class referred to as "multiple malformations." No reports of ethnic differences in the frequencies of chromosomal aberrations have come to our knowledge, and in the present sample the two relevant classes show a fairly uniform distribution among the different communities. It may, however, be worth while to collect further data on the incidence of Mongolism in the Middle East communities, where it appears to be *rarer* than in the other groups. The opposite would be expected in view of the high average parity in these communities and its inevitable correlation with maternal age. This difference should be explored in samples of larger size.

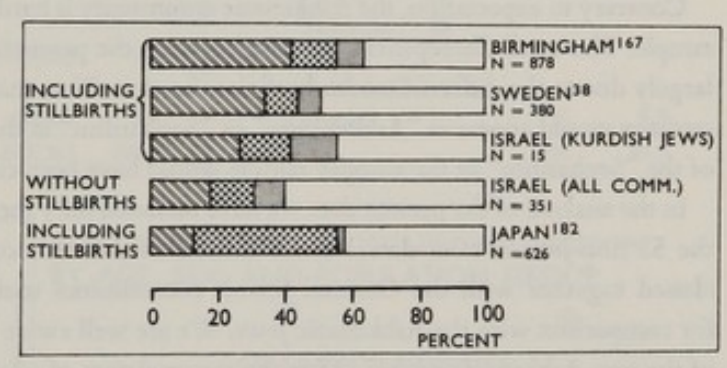


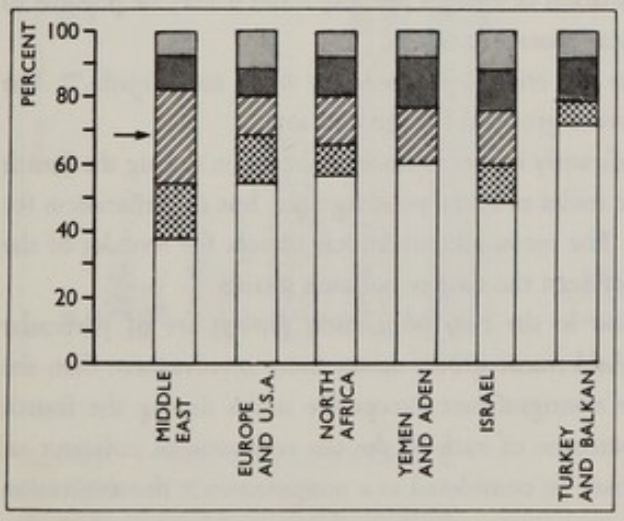
RATES OF MALFORMATIONS AND OF CONSANGUINEOUS MARRIAGES

A: EUROPE AND U.S.A.
B: TURKEY AND BALKAN
C: NORTH AFRICA
D: YEMEN AND ADEN
E: MIDDLE EAST

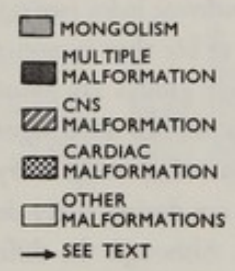
TYPES OF MAJOR MALFORMATIONS IN ISRAEL AND SOME OTHER COUNTRIES





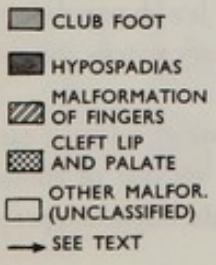


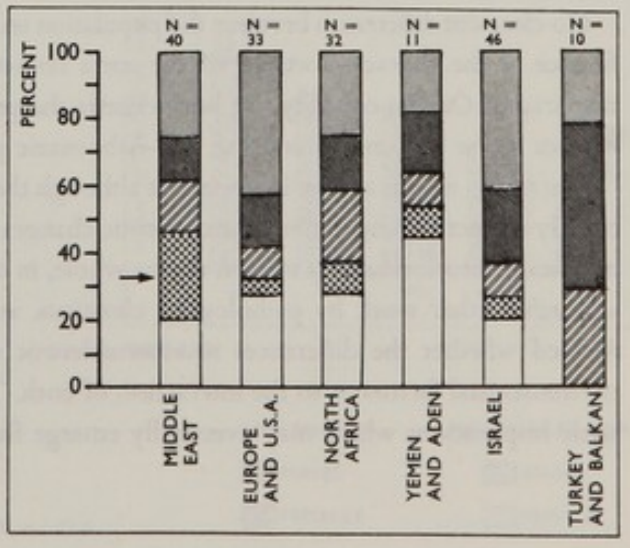
TYPES OF MAJOR MALFORMATIONS IN DIFFERENT JEWISH GROUPS



THE FREQUENCY OF EACH TYPE IS GIVEN AS PERCENTAGE OF ALL MAJOR MALFORMATIONS

FURTHER CLASSIFICATION OF TYPES POOLED AS "OTHER MALFORMATIONS" IN PREVIOUS HISTOGRAM





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ATHEROSCLEROSIS OF THE aorta and the coronary arteries of the heart was studied in 895 consecutive autopsies of adults of both sexes, 30 years and older.[252] The autopsies were performed in three pathology departments in Israel, but the lesions in the heart and the aorta have been evaluated by the same team of workers in Jerusalem. In the table the ethnic composition of this autopsy sample is compared with that of the total population of Israel in the corresponding age groups. The demographic data have been compiled from the official statistics[18] for 1957 and 1958, the years immediately preceding the present survey. The ethnic composition of the autopsy sample agrees remarkably well with that of the general population.

Contrary to expectation, the Ashkenazic community is hardly over-represented in the post-mortem sample. The small discrepancies existing between the percentages in columns 3 and 6 of the table are largely due to the different methods of classification. Thus many of the Israel-born Jews of the official statistics would appear as "Ashkenazim" or "Sephardim" in the autopsy sample. And a certain fraction of the "Sephardim" of the autopsy sample would have been classed officially as born in Asia or Africa.

In the analysis of the present data we have included only the 842 cases of Jewish post-mortems, since the 53 non-Jewish cases derive from a series of different communities. The Sephardic Jews were classed together with the Oriental Jewish communities under the heading of "Non-Ashkenazim" for comparison with the Ashkenazic Jews. We are well aware of the ethnic and cultural heterogeneity of the non-Ashkenazic sample. After the accumulation of a larger autopsy series it may be possible to investigate each non-Ashkenazic community as a separate entity.

The evaluation of the material was based on the criteria proposed by Gore and Tejada.[104] The samples of Ashkenazim and non-Ashkenazim were grouped by age and sex.

The *mean atherosclerotic index* (see right) is significantly higher in male Ashkenazim during the fourth and fifth decades of life than in non-Ashkenazic males of corresponding ages, but the differences for males of higher age groups are nonsignificant. The mean atherosclerotic indices for females of the various age groups do not differ significantly between the two population sectors.

The comparisons of *coronary artery involvement* in the two population groups are of particular interest. For each sex during every decade the Ashkenazic group shows more involvement than the non-Ashkenazim. Although the differences are nonsignificant except for males during the fourth decade and for females during the sixth, the outcome of each of the ten comparisons indicates an advantage of the non-Ashkenazic group. This may be considered as a nonparametric demonstration of a significant difference (see histogram).

No clear-cut differences between the population sectors emerge from the comparisons of the circumference of the thoracic aorta or of the aorta retraction following transverse sectioning below the diaphragm. On the contrary, by both criteria the progressive age changes appear to follow parallel courses in the Ashkenazic and the non-Ashkenazic groups (see histogram).

The results of this survey indicate that although the two major sectors of the Jewish population are equally subject to progressive atherosclerotic changes of the aorta and the coronary system, the course of atherosclerotic disease is milder, on the whole, in the non-Ashkenazic group.

Much further work by pathologists, clinicians, and sociologists will be required before it can be decided whether the differences in atherosclerotic morbidity and mortality are due to ethnic or environmental factors or to the interaction of both. There is no need to stress the important prophylactic implications which may eventually emerge from such studies.*

* This research was supported by Grants H-3942 and H-3942(C-1) from the National Heart Institute, U.S. Public Health Service.

In Cooperation with: B. Gellei H. Karplus E. Liban

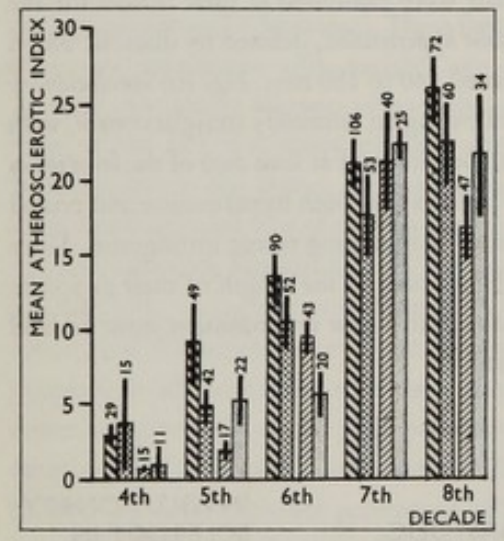
ISRAEL'S POPULATION AGED 30 AND OVER

Official classification	*Number*	%
1. Jews by continent of birth		
Europe and America	505,877	60.8
Africa	77,578	9.3
Asia	142,054	17.1
2. Jews born in Israel	43,766	5.2
3. Moslems, Christians, Druses	62,988	7.6
Total	832,263	100.0

AUTOPSY SAMPLE

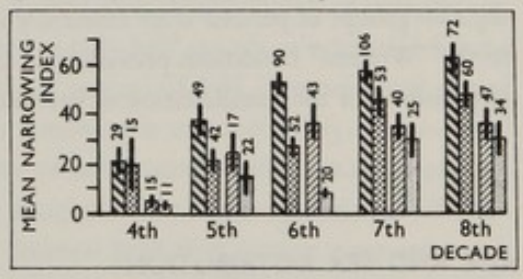
Community	*Number*	%
a. Ashkenazim	568	63.4
b. Sephardim	94	10.5
c. N. African	58	6.5
d. Asian	122	13.6
Middle East 87		
Persian 15		
Yemenite 20		
e. Moslems, Christians, Druses	53	5.9
	895	99.9

AORTA: MEAN ATHEROSCLEROTIC INDEX[104] BY AGE, SEX, AND POPULATION GROUP

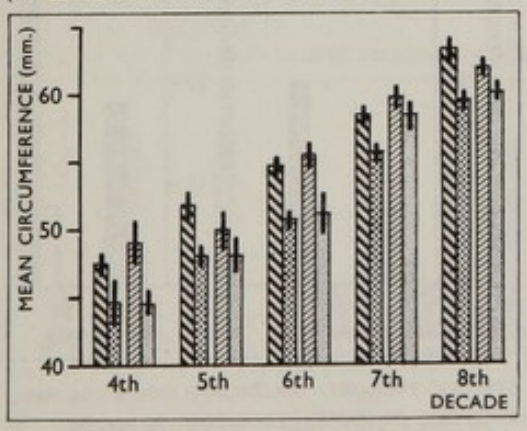


842 AUTOPSY CASES

CORONARY ARTERIES: MEAN INVOLVEMENT[104]
(ASSESSED BY LUMINAL NARROWING IN FIVE SEGMENTS OF THE THREE MAIN BRANCHES)

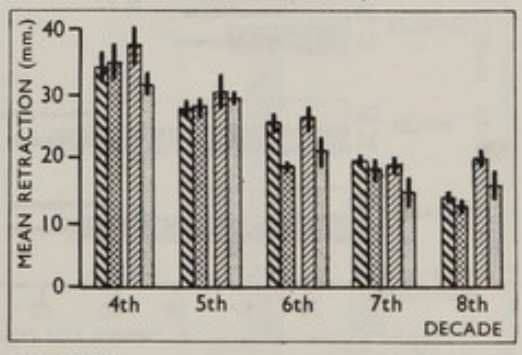


AORTA: MEAN CIRCUMFERENCE OF THORACIC AORTA
(AT LEVEL OF FIFTH INTERCOSTAL ARTERIES)



807 CASES

AORTA: MEAN RETRACTION
(FOLLOWING TRANSVERSE SECTIONING BELOW DIAPHRAGM[104])



508 CASES

ASHKENAZIM — MALES, FEMALES
NON-ASHKENAZIM — MALES, FEMALES

FIGURES ABOVE COLUMNS: NUMBER OF CASES

HEIGHTS OF BLACK BARS IN ALL HISTOGRAMS INDICATE ± 1 ST.E.

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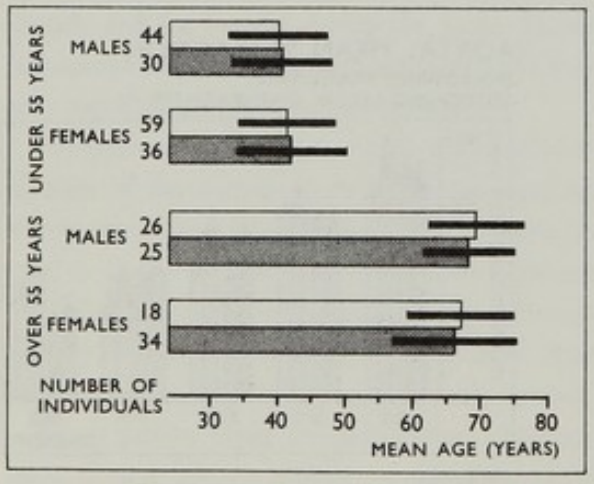
INVOLUTIONARY SCLEROSIS AND DIASTOLIC HYPERTENSION IN YEMENITES

A. M. Cohen E. Neumann I. C. Michaelson

Several teams of investigators[46,76,80] have reported that chronic involutionary disorders such as arteriosclerosis and diabetes are rarely seen in recent immigrants from Yemen, but are fairly common in members of the same community who have resided in Israel for many years. These studies, which were mainly based on hospital statistics, could be subject to some bias if long-time residents were more inclined than new immigrants to apply for hospitalization or more successful in gaining admission to the wards.

It was therefore decided to study two unselected samples of the Yemenite community in a house-to-house survey.[60] The sample of "recent immigrants" comprised the entire population, over the age of thirty, of two settlements situated in the Jerusalem corridor. These persons had arrived from Yemen within the last ten years. The control group of "old residents" comprised all Yemenite Jews over the age of thirty settled in two quarters of Jerusalem. All subjects included in the latter group had lived in Israel for more than 25 years. As indicated in the diagram (below), the two samples showed good agreement in the distribution of age and sex. All individuals were examined at their homes for the following criteria of chronic involutionary disease: (a) *diastolic hypertension*, defined by diastolic blood pressure exceeding 90 mm. Hg when systolic pressure exceeded 140 to 150 mm. Hg. (b) *involutionary sclerosis of the retina*, recognized by narrow retinal arteries, following an unusually straight course, with narrow bifurcations. Sclerosis of the retina was considered to be present if at least two of the four main vessels of each fundus were affected. The histogram (below) shows that both hypertension and retinal sclerosis were significantly more prevalent among "old-timers" than among recent immigrants. Since the two groups of persons were ethnically identical and differed only in the length of their exposure to the "Western" conditions prevailing in Israel, some factors of this new environment must be held responsible for the manifestation of involutionary disorders.

AGE AND SEX DISTRIBUTION OF INDIVIDUALS TESTED



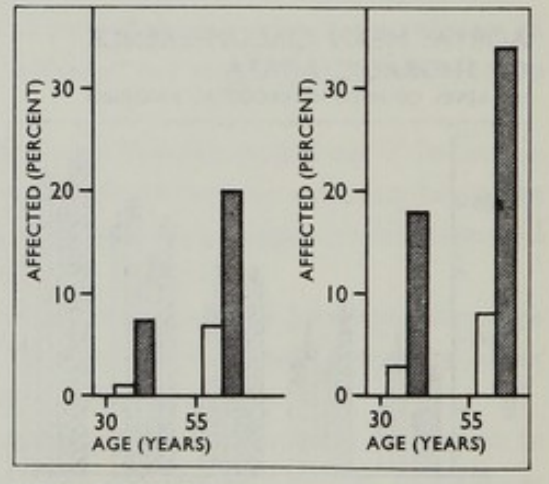
IMMIGRATED TO ISRAEL WITHIN LAST 10 YEARS

SETTLED IN ISRAEL FOR LAST 25 YEARS (OR ISRAEL-BORN)

LENGTH OF BLACK BARS INDICATE ±1 ST.E.

DIASTOLIC HYPERTENSION

INVOLUTIONARY SCLEROSIS IN THE RETINA



SYSTOLIC PRESSURE: EXCEEDING 140-150 mm. Hg.

DIASTOLIC PRESSURE: EXCEEDING 90 mm. Hg.

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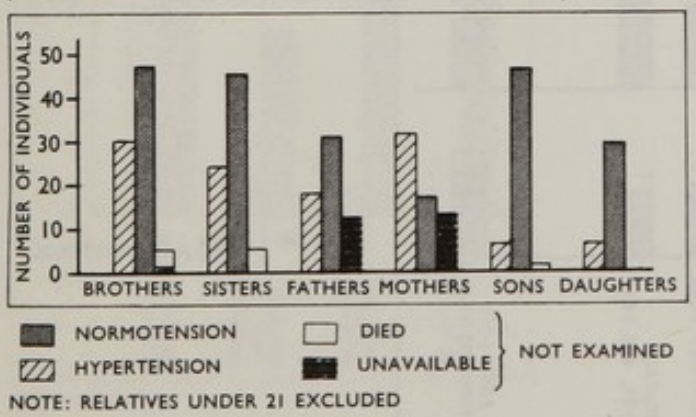
THE MATERIAL here presented is a preliminary report on a study undertaken to throw light on the following questions: (1) Is essential hypertension (E.H.) the manifestation of a single gene behaving as a Mendelian dominant, as suggested by Platt,[192] or is the condition, as Pickering believes, a quantitative and not a qualitative deviation from the normal?[186] (2) Is there any difference in predisposition to familial E.H. between Jews of Ashkenazic and those of Oriental origin?

According to the definition adopted by us, essential hypertension is a persistent diastolic blood pressure of 90 mm. Hg or more in subjects aged 21 to 50 years and of 95 mm. Hg or more in subjects over 50 years of age. This study is based on 109 propositi with E.H. who visited our clinic. They had in all 732 first-degree relations aged 21 or more, in 696 of whom the blood pressure level was known. In 61 families one or several first-degree relations of the propositus were found to suffer from E.H. In another 48 families, among 366 first degree relations of the propositus, no affected subjects have been found.

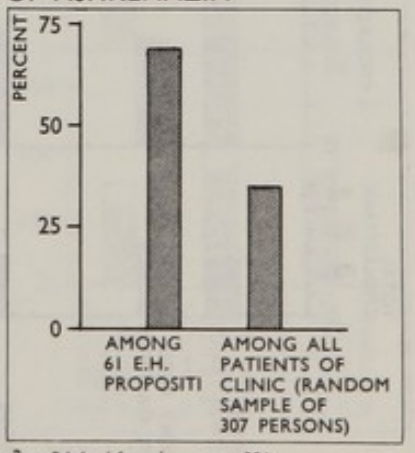
The histogram (below) shows that the prevalence of E.H. amounted to 50.5 percent among the *investigated* parents of propositi and to 42.4 percent among their investigated sibs but was much lower in their offspring (13.8 percent). These figures are in good agreement with the hypothesis of autosomal dominant inheritance with variable age of onset. Almost exactly 50 percent were affected in the parental generation, whereas among sibs and offspring the incidence is lower, as would be expected in view of the fact that many of these persons are still comparatively young and may yet develop hypertension in the future. Although the distinction between familial and sporadic E.H. may be considered artificial, it is of interest that the average age of our sporadic cases was higher than that of the propositi with familial E.H. When pooling the data on the investigated relatives of sporadic and familial E.H., we obtain prevalence rates which are approximately half as high as calculated for the relatives of the familial cases alone. An incidence of 20 to 25 percent of E.H. in parents and sibs of propositi is still consistent with the assumption that this condition is transmitted by an autosomal dominant gene with incomplete penetrance, but a variety of other interpretations may be offered. Among the 61 propositi with familial E.H. there was a significantly higher percentage of Ashkenazic Jews and a smaller percentage of Sephardic and Oriental Jews than among a representative sample of the population attending the general medical clinic from whom the propositi were taken (see diagram).

BLOOD PRESSURE IN FAMILIES OF 61 E.H. PROPOSITI
(WITH ONE AFFECTED FIRST DEGREE RELATIVE OR MORE)



NOTE: RELATIVES UNDER 21 EXCLUDED

REPRESENTATION OF ASHKENAZIM



$\chi^2 = 24.4$, d.f. = 1 $p < .001$

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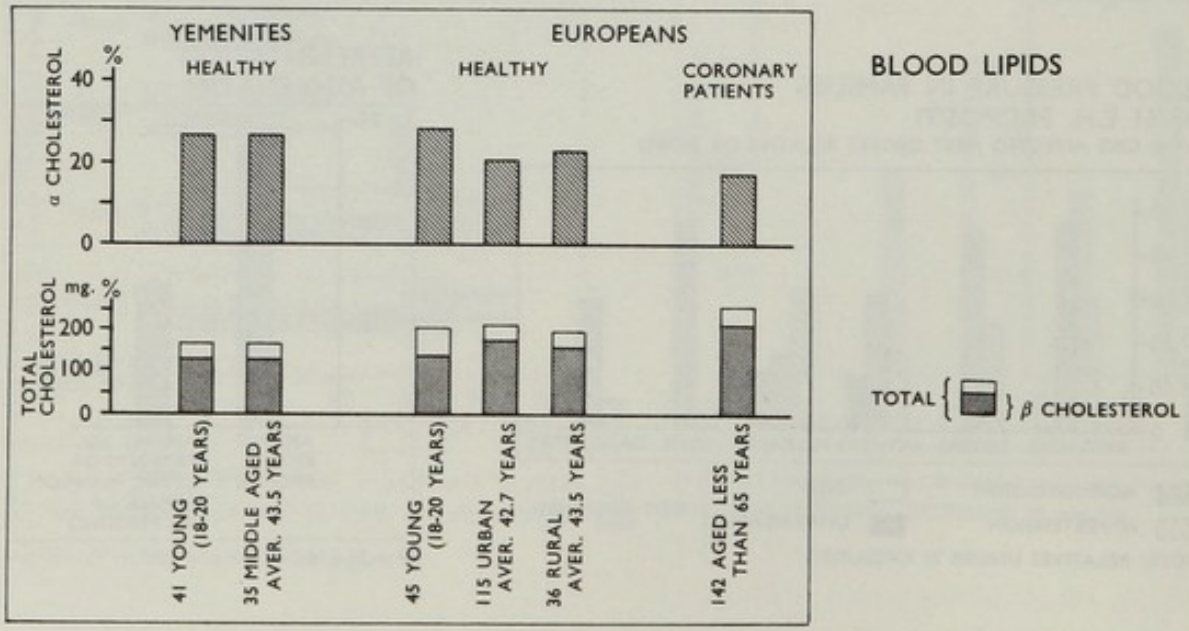
A CHARACTERISTIC AGE CHANGE in blood lipid pattern has been demonstrated in various population groups[83, 140] (see also p. 131) including even the Bantus.[255] The progressive rise in cholesterol level is considered by many authorities as the expression of an inevitable aging process, from which no healthy person is exempted. There is, on the other hand, much evidence supporting a correlation between high cholesterol level in the blood and atherogenic activity in the vascular walls. Indeed, the lipid pattern is believed to have prognostic significance and is widely used as a basis for detecting the potential victim of ischemic heart disease.

It was felt that for any given population an accurate definition of a "pathological" lipid pattern required a thorough study of the "normal" age changes in blood cholesterol. We have therefore compared the cholesterol levels of young and of middle-aged individuals in two Jewish groups in Israel[48]—Ashkenazim, among whom myocardial infarction is as common as in other Western populations, and Yemenites,[43, 44] who suffer only rarely from coronary disease.

The results of these studies are summarized in the histogram (below). Although total cholesterol level may be positively correlated with atherogenic activity, we have reason to rely even more on the relative content of α-cholesterol,[45] which exhibits a negative correlation with occlusive vascular disease. The diagram indicates that, in middle-aged Ashkenazim, the blood lipids exhibit a rise in total cholesterol and a relative decrease in α-cholesterol. This change, which is reminiscent of the grossly distorted pattern characteristic of coronary heart patients (see diagram) is much more pronounced in an urban group of Ashkenazim than among rural settlers (kibbutz members), who are mostly engaged in hard physical labor and among whom myocardial infarctions are uncommon.[47] No similar change is apparent in middle-aged Yemenites, whose lipid pattern is almost identical with that of young persons of the same community. We are inclined to assume that the middle-aged Yemenite may owe his "youthful" lipid pattern to certain features of his mode of life.



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DEGENERATIVE VASCULAR changes are far commoner in diabetic patients than in the general population. Many authorities therefore tend to assume a causal connection between atherosclerosis and the hormonal defect in diabetes. It seemed of interest to investigate whether this correlation manifests itself with equal intensity in all diabetics, irrespective of social and ethnic background.

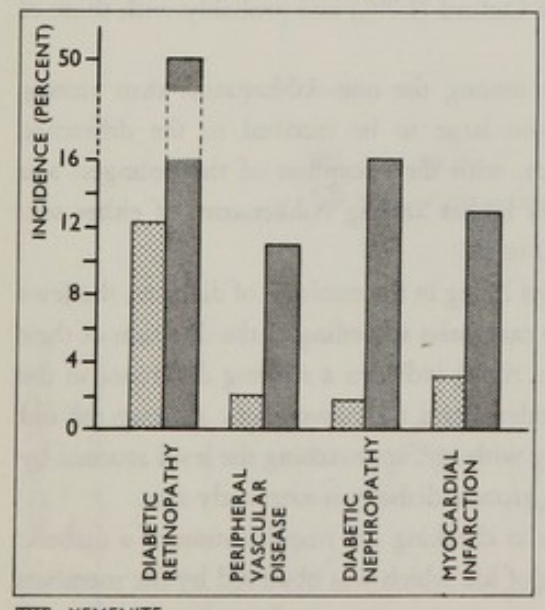
This problem can be studied with advantage in the Yemenite Jews, among whom ischemic heart disease is much rarer than among European Jews or other Western groups. Although the Yemenites are also notable for their low diabetes rate, we have been able to assemble 76 Yemenite diabetics. We have subjected these patients to a thorough physical examination[43] including EKG, X-ray study of chest and of abdominal aorta, and eye ground examination. The blood serum of each case was tested[44] for urea, total serum proteins, and lipid pattern.

The incidence of various pathological conditions of the vascular system proved to be much lower in these patients than in a group of diabetics studied by Byfogle and Bradley[50] in the United States (see diagram, left below). Thus, retinopathy, which heads the list of vascular complications in diabetes, was four times commoner among Americans than among Yemenites.

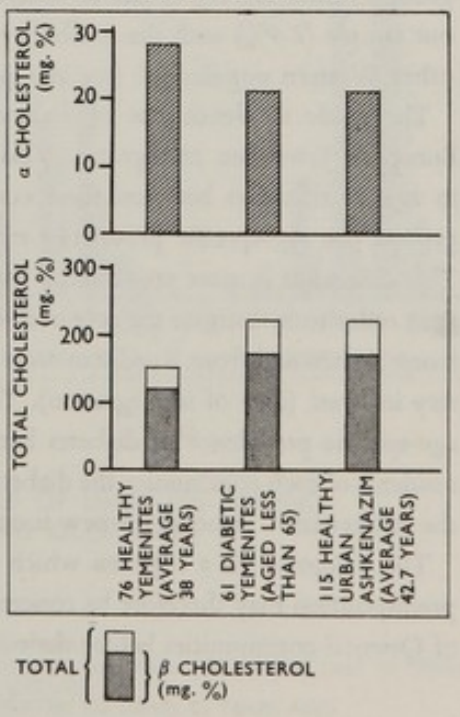
It has been demonstrated (see also p. 131) that the blood lipids of healthy middle-aged Yemenites maintain the pattern characteristic of young adults. They fail to exhibit the rise in total cholesterol and the drop in relative content of α-cholesterol which marks the onset of middle age in the average European Jew. The histogram (below, right) shows that the diabetic Yemenite resembles the middle-aged healthy Ashkenazim in lipid pattern and differs from normal Yemenites of his age group.

The lipid pattern of the diabetic Yemenite reflects his increased risk of vascular disease. However this risk is clearly lower than in diabetics of Western origin. Thus the association between vascular degeneration and hormonal disturbance varies in extent between different ethnic groups and can hardly be due to a primary correlation at the biochemical level.

PATHOLOGICAL FINDINGS IN YEMENITE AND U.S. DIABETICS



BLOOD LIPIDS IN HEALTHY AND DIABETIC YEMENITES



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DIABETES MELLITUS is generally assumed to result from the interaction of a predisposing genotype with a specific set of environmental conditions. Nevertheless, the geographic epidemiologist, when faced with a marked variation in diabetes incidence among different social and ethnic groups, is only rarely in a position to estimate the relative importance of the intrinsic and extrinsic factors that give rise to this variation. The present composition of the population in Israel offers an excellent opportunity to study the nature-nurture problem in diabetes. For many members of the Oriental Jewish communities, the immigration to this country entails profound changes in mode of life and nutrition. It is therefore possible to compare population samples that are ethnically identical and differ only in the length of their exposure to a "Western" environment.

The incidence of diabetes in Israel was studied[59] in a house-to-house survey of 23 rural settlements and several quarters of Jerusalem. After a complete registration of all families living in the area, labeled test tubes were distributed with instructions to collect the postprandial urine of each family member. The urine was tested with glucose reductase. For positive cases, blood sugar tests, and, if necessary, glucose tolerance tests, were performed in addition. Persons exhibiting glucosuria and fasting blood sugar higher than 120 mg. percent were classified as diabetics.

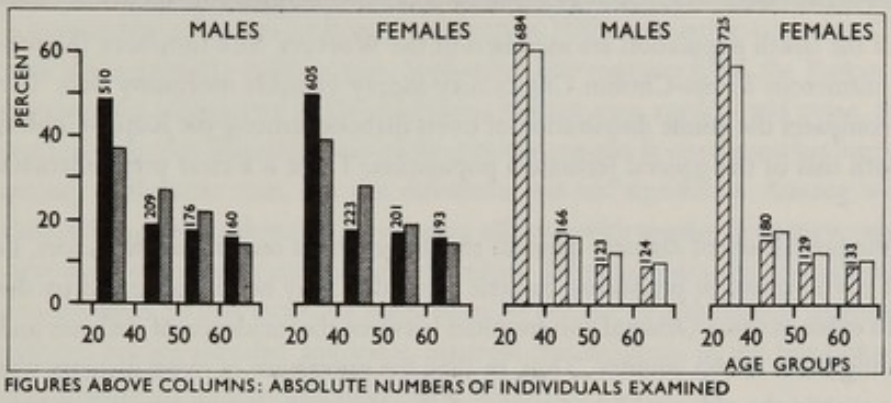
The total sample, which comprised 15,958 persons, was broken up into four major ethnic subgroups: Kurdish Jews, Yemenite Jews, Ashkenazim, and all other communities—classed together as "non-Ashkenazim."

The age stratification of the Ashkenazic and the non-Ashkenazic subsamples was compared with that registered in the official statistics for the general population of these communities. As seen from the histogram (top) the agreement was very good, on the whole, and these samples may therefore be considered as representative of their ethnic groups. It is also of interest to compare the age distribution of the present sample with that of the U.S. population studied by Wilkerson and Krall[261] (see histogram). Although the age stratification of Ashkenazim resembles that of Oxford in the United States,[261] the non-Ashkenazim differ from either by a somewhat sparser representation of the older age groups. Hence it is legitimate to compare the crude prevalence rate of diabetes in the Ashkenazim of our sample (2.4%) with the morbidity rate recorded for Oxford (1.7%) and probably with those of other Western populations (see also p. 127).

The crude incidence rate of diabetes is much lower among the non-Ashkenazim than among European Jews (see histogram). This discrepancy is too large to be ascribed to the difference in age stratification between these communities. In fact, with the exception of the youngest age groups, the age-specific prevalence rates are consistently higher among Ashkenazim of either sex. This difference is most pronounced for women aged 50 to 59.

In order to investigate the role of a Western standard of living in the etiology of diabetes, the Jews from Yemen and from Kurdistan were divided into two categories according to the duration of their stay in Israel (date of immigration). The graph (bottom right) indicates a striking difference in the age-specific prevalence of diabetes between the old residents and the newcomers. Among the old residents of each community the diabetes rate rises steeply with age, approaching the level attained by the Ashkenazim. Among the new immigrants of all age groups, diabetes is extremely rare.

The blueprint for a regimen which is highly efficient in checking the manifestation of a diabetic predisposition may therefore be concealed in the pattern of life which was observed by the members of Oriental communities before their immigration.

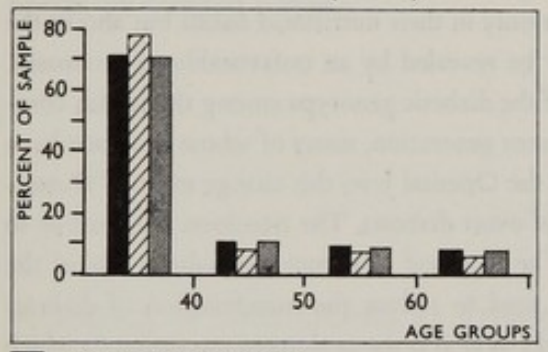


AGE DISTRIBUTION AMONG ADULTS OF PRESENT SAMPLE (1958-1959) AND OF GENERAL POPULATION (1957)

ASHKENAZIM
SAMPLE
OFFICIAL STATISTICS
NON-ASHKENAZIM
SAMPLE
OFFICIAL STATISTICS

FIGURES ABOVE COLUMNS: ABSOLUTE NUMBERS OF INDIVIDUALS EXAMINED

AGE DISTRIBUTION AMONG ADULTS OF THE PRESENT SAMPLE AND AMONG U.S. CITIZENS (MASS.)[261]

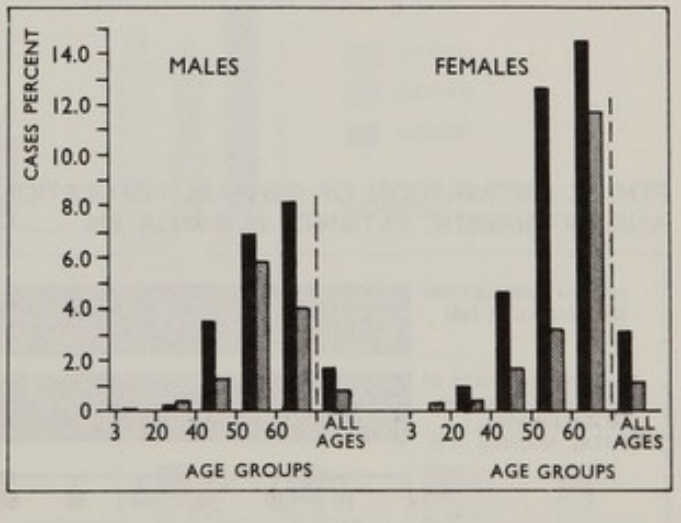


ASHKENAZIM (4,344 IND.)
NON-ASHKENAZIM (4,156 IND.)
OXFORD (MASS.) (3,516 IND.)

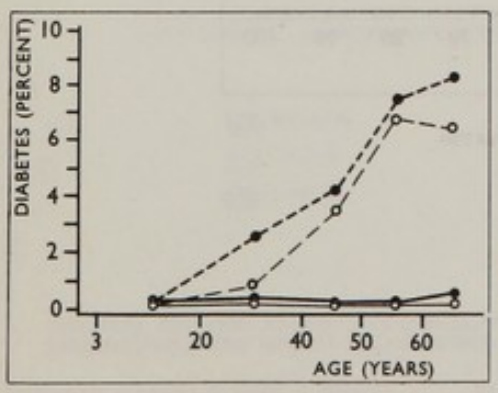
Ashkenazim:	*Number tested*
	2065 males
	2279 females
Non-Ashkenazim:	*Number tested*
(excluding Yemenite and Kurdish Jews)	2123 males
	2033 females

Source: Wilkerson and Krall,[261] 1947.

PREVALENCE OF DIABETES ACCORDING TO AGE AND SEX



ASHKENAZIM
NON-ASHKENAZIM



THE PREVALENCE OF DIABETES AMONG NEWCOMERS AND OLDTIMERS

KURD. JEWS — YEMENITE JEWS

NEW IMMIGRANTS: IMMIGRATED TO ISRAEL WITHIN THE LAST 10 YEARS
OLD SETTLERS: IMMIGRATED TO ISRAEL 25 YEARS AGO OR BORN IN ISRAEL

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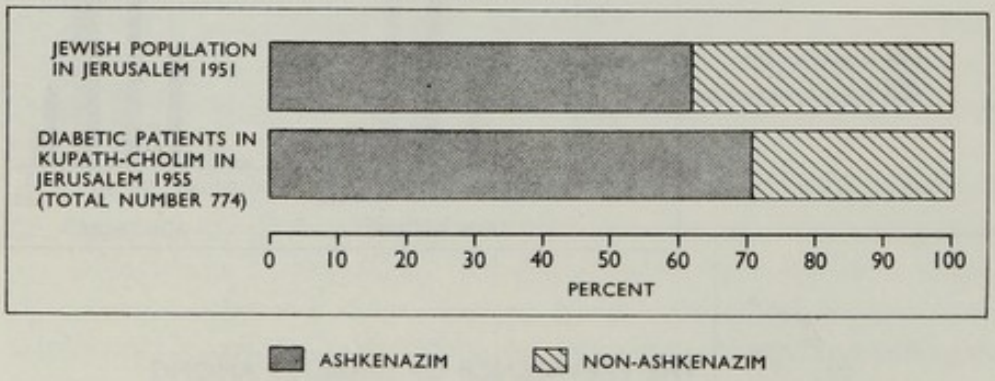
SINCE A LARGE majority of the Israeli population are members of the Workers' Sick Insurance (Kupat-Cholim), the files of the numerous Kupat-Cholim Clinics may supply valuable morbidity data. The accompanying diagram compares the ethnic distribution of overt diabetics among the Kupat-Cholim members of Jerusalem with that of the general Jerusalem population. There is a clear preponderance of Ashkenazic cases.[183]

It is well known that the prevalence of diabetes depends to a large extent on nutritional factors. In Israel the decisive role of environment in producing diabetic morbidity may be demonstrated by the positive correlation which exists in some Oriental communities between the incidence of diabetes and the time elapsed after immigration to this country. Thus, in 1956 the prevalence of overt diabetes was estimated at 0.62 percent among the old, established sector of the Yemenite population and at only 0.22 percent among Yemenites who had entered the country after 1948.[184] This estimate was based on a country-wide survey of diabetes clinics affiliated to Kupat-Cholim and other medical institutions.

It is entirely possible that the communities differ not only in their nutritional habits but also in the concentration of the susceptible genotype which may be revealed by an unfavorable environment. However, if there were a heterogeneous distribution of the diabetic genotype among the Jewish communities, we could hardly hope to reveal this in the present generation, many of whose members have experienced some major change in pattern of life. For the Oriental Jews this change meant "Westernization," which has been shown to increase the rate of overt diabetes. The transition from urban to rural life experienced by many Ashkenazic Jews may be expected to reduce the diabetes rate of the present generation. An additional factor which may tend to reduce the manifestation of diabetes among Ashkenazic immigrants who arrived after World War II is the prolonged starvation to which many of these persons were subjected in concentration camps.

ETHNIC DISTRIBUTION OF GENERAL POPULATION AND OF DIABETIC PATIENTS IN JERUSALEM



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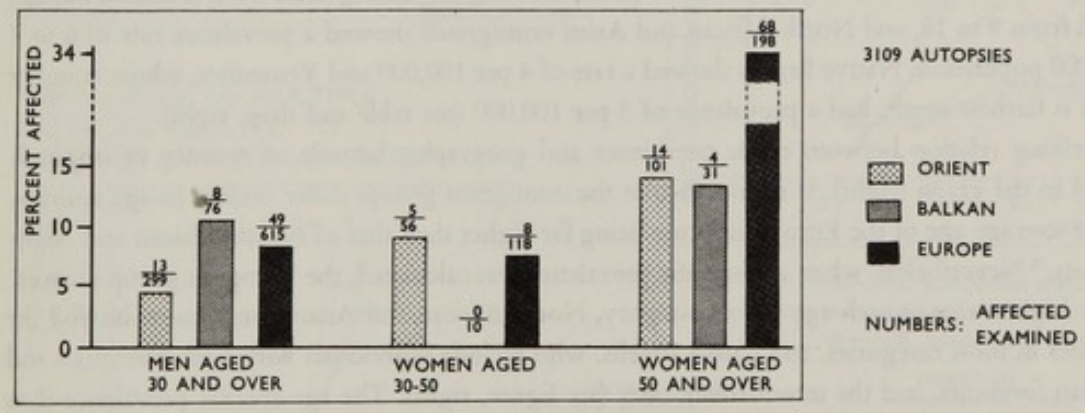
Kupath Cholim
Jerusalem, Israel

D. Brunner S. Altman K. Loebl G. Manelis H. Karplus

A SEARCH FOR gallstones has been carried out in 3109 consecutive autopsies. Three major ethnic groups were distinguished—Ashkenazim, Sephardim (immigrants from the Balkan countries), and all other communities, designated as Oriental Jews. Among men aged 30 and more, the incidence of gallstones was lowest in the Oriental group of the autopsy sample. It was somewhat higher among Sephardic than among Ashkenazic men, but this difference was not significant. Among women aged 30 to 50, the Oriental and the Ashkenazic group were affected with similar frequency, whereas the Sephardic cases were too few to justify conclusions. A striking difference between the communities is apparent among women aged 50 and more. In more than 30 percent of Ashkenazic women of this age group post-mortem studies revealed gallstones, whereas the incidence in the remaining population sectors was only around 12 percent (see histogram, below).

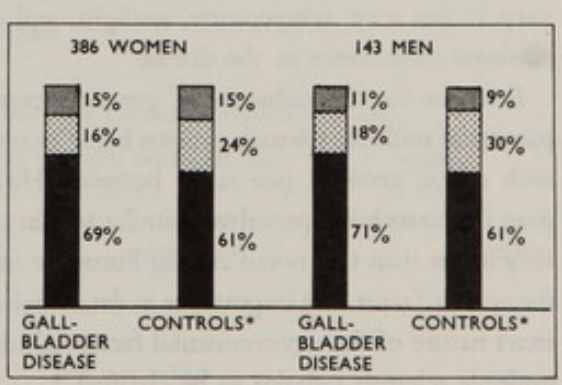
These autopsy findings are in good agreement with hospital statistics indicating an over-representation of Ashkenazim among gall-bladder patients and a relative scarcity of gall-bladder disease among the Oriental groups.

INCIDENCE OF GALL-STONES BY ETHNIC GROUP



ETHNIC DISTRIBUTION OF GALL-BLADDER PATIENTS

529 GALL-BLADDER PATIENTS COMPARED WITH GENERAL HOSPITAL POPULATION



ORIENTAL MEN AND WOMEN ARE SIGNIFICANTLY UNDERREPRESENTED AMONG GALL-BLADDER PATIENTS

*CONTROLS FROM GENERAL HOSPITAL POPULATION WERE MATCHED REGARDING SEX, AGE AND DATE OF IMMIGRATION

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THE PREVALENCE OF MULTIPLE SCLEROSIS AMONG IMMIGRANTS AND ISRAELIS

IT IS WIDELY believed that the prevalence of multiple sclerosis decreases from temperate to tropical areas.[9, 130, 146] However, the evidence for this assumption is incomplete, as estimates of multiple sclerosis prevalence are still lacking from many parts of the world—*e.g.*, Asia, Africa, and most of the Southern Hemisphere. Moreover, because existing data have not been collected by a uniform technique, estimates from different areas are not necessarily comparable.

In order to determine the number of patients with multiple sclerosis living in Israel on January 1, 1960, medical records were reviewed in all hospitals and central clinics for the period 1954 through 1959. In addition, the records of the Central Bureau of Statistics were studied and physicians with private neurological practices were queried. The private physicians contacted numbered 27 and included all those who by reputation see neurological as well as psychiatric patients. Five diseases clinically similar to multiple sclerosis (paraplegia, primary lateral sclerosis, retrobulbar neuritis, cerebellar ataxia, myelopathy) were also included in order to identify cases listed possibly under different diagnostic labels.

Two categories of patients were accepted: probable cases, usually including those with remissions and exacerbations and evidence of scattered neurological deficit; and possible cases, usually including those with progressive course and inadequate evidence of scattered signs.

Of 1000 cases identified, 282 were accepted. The prevalence of multiple sclerosis in Israel based on the accepted cases is 15 per 100,000 population. The prevalence was estimated for immigrants from different countries of origin and it was found that prevalence of multiple sclerosis declined among the immigrants the farther south their country of origin. Among northern and central European immigrants the prevalence per 100,000 population ranged from 30 to 51, among those from southern Europe it ranged from 9 to 18, and North African and Asian immigrants showed a prevalence rate of 6 to 7 per 100,000 population. Native Israelis showed a rate of 4 per 100,000 and Yemenites, whose country of origin is farthest south, had a prevalence of 3 per 100,000 (see table and map, right).

The striking relation between crude prevalence and geographic latitude of country of origin is illustrated in the graph (right). It is known that the immigrant groups differ widely in age composition, the average age of the European sector being far higher than that of North African and Asian immigrants.[18] Nevertheless, when age-specific prevalence was calculated, the European group showed again the highest rate in each age-group category, North African and Asian immigrants showed the lowest rates in most categories, and native Israelis, who include individuals with both European and Afro-Asian forebears, had the intermediate rates (see figure, right). The age-specific prevalence thus supports the hypothesis that an environmental factor which varies with latitude is responsible for determining the geographic distribution of multiple sclerosis. Among environmental factors which vary in this way, temperature, sunlight, and dietary fat have been suggested as possibly being of etiologic importance in the disease.[1]

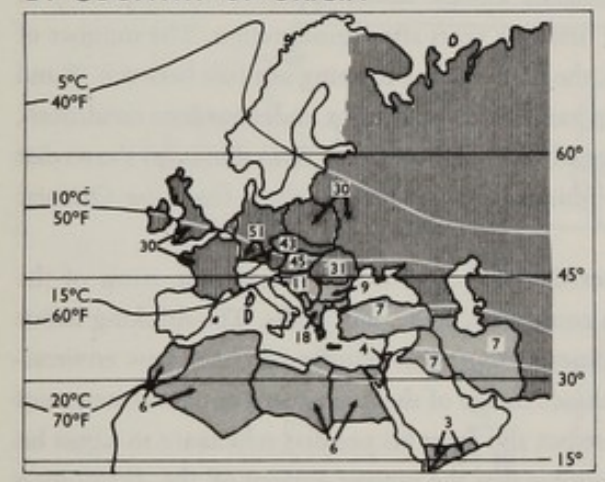
Evidence for the influence of genetic factors[8] was also obtained, the consanguinity rate among parents of multiple sclerosis patients being two to three times higher than in the general population of each ethnic group[103] (see table, bottom). However, the fact that native-born Israelis with European forebears had a prevalence similar to that observed among Afro-Asian immigrants and considerably lower than that noted among European immigrants suggests that the environmental rather than the genetic factor is of importance in determining the prevalence of the disease in a particular area. The exact nature of the environmental factor which accounts for the peculiar geographic distribution of multiple sclerosis remains to be clarified.*

* The authors are greatly obligated to Dr. Leonard Kurland for his interest and encouragement.

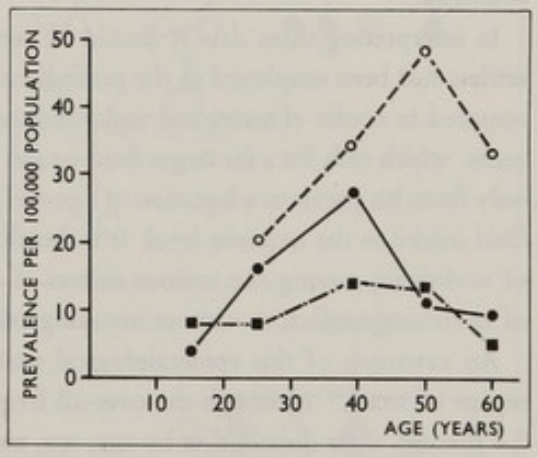
THE PREVALENCE OF MULTIPLE SCLEROSIS AMONG IMMIGRANTS AND NATIVE ISRAELIS

Area of origin	*Population*	*No. of cases*	*Prevalence per 100,000 population*
Europe	656,000	208	33
Middle East and North Africa	428,000	33	8
Israel	588,000	25	4
Yemen	63,000	2	3
Unknown	—	14	—
Total	1,735,000	282	

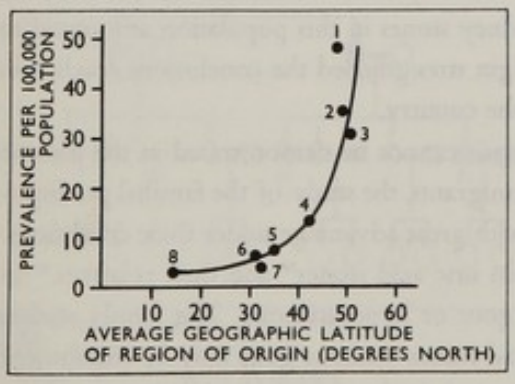
PREVALENCE OF MULTIPLE SCLEROSIS BY COUNTRY OF ORIGIN



AGE SPECIFIC PREVALENCE RATES BY REGION OF ORIGIN



PREVALENCE OF MULTIPLE SCLEROSIS RELATED TO LATITUDE OF BIRTH-COUNTRY



CONSANGUINITY RATES AMONG PARENTS OF MULTIPLE SCLEROSIS PATIENTS IN ISRAEL

	EUROPE			MIDDLE EAST AND NORTH AFRICA			ISRAEL		
	No.	*Percent*		*No.*	*Percent*		*No.*	*Percent*	
		Patients	*General population*		*Patients*	*General population*		*Patients*	*General population*
Total with multiple sclerosis	208			49			25		
Total offspring of consanguineous parents	12	10.1	2.4	11	22.4	14.8	2	8	?
Offspring of first cousins and closer relatives	14	6.8	1.4	9	18.4	8.8	—	—	?

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A MAJOR EPIDEMIOLOGICAL problem facing the urologist in Israel is the high incidence of urolithiasis. Although the rate of affection with kidney stones in the United States has been estimated at 0.947 per thousand,[39] the incidence of this disorder in Israel has been reported[93] to be about ten times higher.

The distribution of this disease was studied in 12 settlements comprising 30,292 inhabitants in all, and situated in climatically different areas of Israel.[93] The over-all frequency of urolithiasis was found to be 1.18 percent. The incidence of urolithiasis by sex, community, and date of immigration was determined. Much of the evidence produced underlines the implication of environmental factors in the etiology of this disorder. Although the average temperature and humidity prevailing in each area appear to exert some influence on the manifestation of kidney stones in the inhabitants, the most decisive role may be attributed to physical exertion, sun exposure, and individual adaptation to these conditions. Among the population of these settlements kidney stones appear most frequently in recently arrived immigrants—generally within the first five years after immigration. The number of cases first diagnosed after the age of 50 is very small, the first attacks occurring as a rule between 18 and 50 years of age. These are the age groups occupied in hard agricultural labor under outdoor conditions, whereas younger and older persons are usually assigned much lighter tasks. The table (top) shows that in immigrants from Europe, the incidence of urolithiasis is higher than in those from the Oriental countries.

In interpreting these data it should be remembered that, before their immigration, most of the settlers had been employed in the professions or in commerce, trade, and crafts. The drinking habits acquired in cooler climates and under indoor conditions were often transferred to the new environment, which calls for a far larger fluid intake. The disadvantage of the European immigrant stems not only from his previous adaptation to a cooler climate but also from his peculiar reluctance to adjust his fluid intake to the requisite level. It is therefore plausible that the present pattern of the distribution of urolithiasis among the various sectors of the Israeli population may be explained as the result of environment factors without invoking any ethnic differences in the predisposition to the disease.

An extension of this epidemiological study included 10,824 persons settled in the hot and arid region of Israel.[92] Although the over-all frequency of kidney stones in this population amounted to 2.4 percent, their distribution by age, sex, and ethnic origin strengthened the conclusions reached in our previous survey in the central and northern part of the country.

Although ethnic differences in the tendency to urolithiasis cannot be demonstrated in the present generation, which comprises such a high proportion of immigrants, the study of the familial predisposition to certain types of kidney stones may be pursued with great advantage under these conditions.

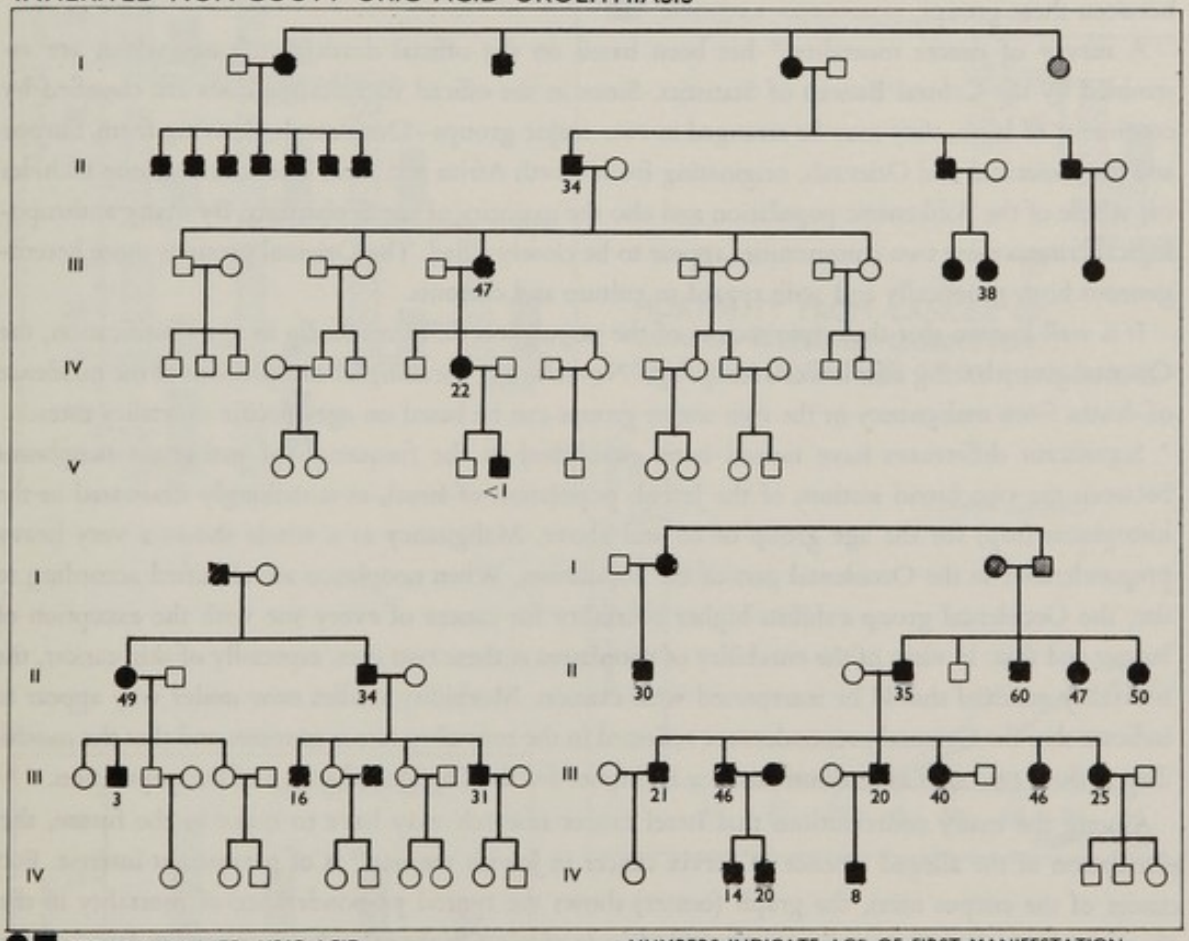
Our team has studied a series of patients suffering from uric acid stones[24] and their relatives.[91] In about 70 percent of the propositi there was no sign of gout or hyperuricemia. The family studies support the assumption that the predisposition to uric acid stones without gout may be transmitted through several generations. In the three pedigrees presented (right center) the inheritance of the disease appears to follow a dominant pattern. Familial non-gouty uric acid urolithiasis has thus far been found among Ashkenazim, Sephardim, and Jews from North Africa and Baghdad.

In a family of Sephardic Jews from Bulgaria we have observed[74] a new type of urolithiasis, associated with the excessive excretion of glycine (see pedigree, right bottom). All affected members of the kinship excreted large amounts of glycine in the urine, whereas the serum concentration was normal. It is therefore clear that this uncommon aminoaciduria is due to an inherited abnormality of the renal tubules which fail to reabsorb glycine. It could also be shown that an intravenous glycine load (1 gm. per 15 lb. body weight) is excreted far more rapidly by a subject suffering from glycinuria than by normal individuals.

UROLITHIASIS ACCORDING TO COUNTRY OF BIRTH AND AGE AT TIME OF INVESTIGATION

	BORN IN ISRAEL			BORN ELSEWHERE						TOTAL		
				Middle East & North Africa			*Europe*					
Age	*Sample size*	*No.*	*Urolith. %*	*Sample size*	*No.*	*Urolith. %*	*Sample size*	*No.*	*Urolith. %*	*Sample size*	*No.*	*Urolith. %*
0-10	6406	—	—	1459	1	0.7	666	—	—	8531	1	0.12
11-17	764	3	3.9	2630	3	1.1	666	—	—	4060	6	1.5
18-30	311	3	9.7	3521	30	9.0	1913	25	13.6	5745	58	10.1
31-40	16	2	—	2194	35	16.4	1444	37	26.4	3654	74	20.2
41-50	2	2	—	1490	15	10.0	1908	90	47.0	3400	107	31.5
51 and over	—	—	—	1741	21	12.0	2108	82	38.8	3849	103	27.0

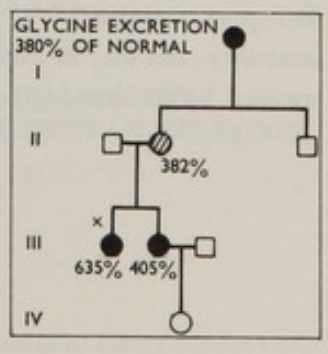
INHERITED NON-GOUTY URIC ACID UROLITHIASIS



STONE EXAMINED, URIC ACID
HISTORY OF UROLITHIASIS
NO INFORMATION AVAILABLE

NUMBERS INDICATE AGE OF FIRST MANIFESTATION. NONE OF THE AFFECTED MEMBERS HAD HYPERURICEMIA AND ONLY TWO HAD HYPERURICOSURIA

GLYCINURIA ASSOCIATED WITH NEPHROLITHIASIS IN A FAMILY OF SEPHARDIC JEWS



GLYCINURIA WITH NEPHROLITHIASIS
GLYCINURIA ONLY

NOTE: ONE STONE EXAMINED FROM PATIENT MARKED X CONTAINED Ca OXALATE AND GLYCINE, THE LATTER CONSTITUTING .5 PERCENT OF THE DRY WEIGHT

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GEOGRAPHIC EPIDEMIOLOGY is expected, in the course of the years, to supply answers where the clinical and experimental approaches have thus far failed to provide satisfactory solutions to etiological problems.

The Jewish communities of Israel differ in ethnic composition, in cultural background, in diet and hygiene, and their members come from countries with diverse climatic conditions. A variety of factors may therefore be responsible for any differences in cancer mortality which may be observed between these groups.

A survey of cancer mortality[135] has been based on the official death certificates which are assembled by the Central Bureau of Statistics. Since in the official statistics the cases are classified by continents of birth, they may be arranged in two major groups—Occidentals, deriving from Europe and the Americas, and Orientals, originating from North Africa and Asia. The former group includes the whole of the Ashkenazic population and also the majority of the Sephardim. By many anthropological criteria these two communities appear to be closely allied. The Oriental group is more heterogeneous both genetically and with regard to culture and customs.

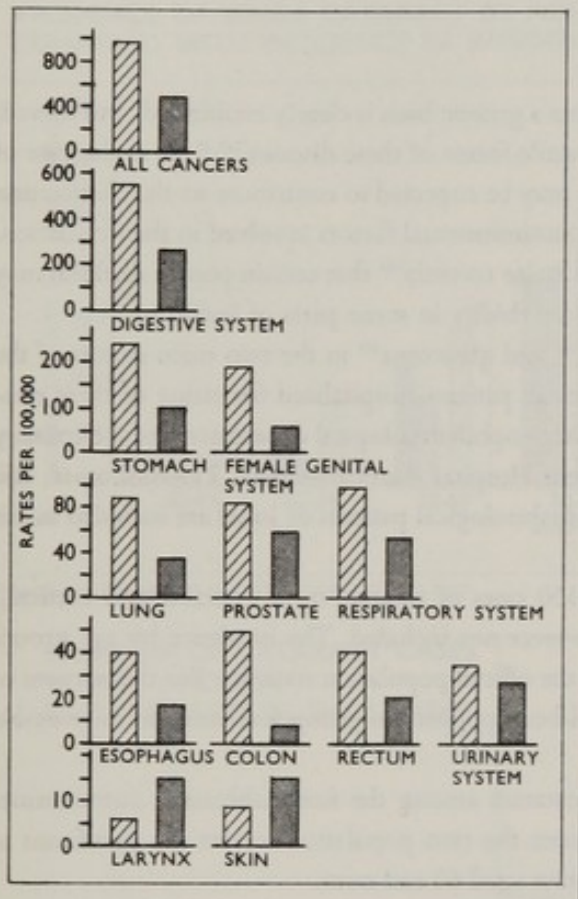
It is well known that these two sectors of the population differ markedly in age stratification, the Oriental group having a far lower average age. Nevertheless, meaningful comparisons of the incidence of deaths from malignancy in the two major groups can be based on age-specific mortality rates.

Significant differences have indeed been established in the frequency of malignant neoplasms between the two broad sections of the Jewish population of Israel, as is strikingly illustrated in the histograms (top) for the age group of 65 and above. Malignancy as a whole shows a very heavy preponderance in the Occidental part of the population. When neoplasms are classified according to site, the Occidental group exhibits higher mortality for cancer of every site with the exception of larynx and skin. In view of the curability of neoplasms at these two sites, especially of skin cancer, the mortality material should be interpreted with caution. Morbidity studies now under way appear to indicate that the Oriental preponderance reflected in the mortality rate is spurious and that the morbidity at these two sites as at all others may be higher for the Occidental sector of the population.

Among the many contributions that Israel cancer research may have to make in the future, the elucidation of the alleged absence of cervix cancer in Jewish women[52] is of paramount interest. For cancer of the corpus uteri, the graph (center) shows the typical preponderance of mortality in the Occidental communities, starting in the fifth decade of life. On the other hand, mortality from cancer of the cervix is very low in all age groups of all population sectors. The cervix-corpus mortality ratio for the total Israeli population is therefore far lower in all age groups than reported for various European countries[14, 15, 16, 17] (see histogram, bottom). It is possible, however, that, in this case, again mortality rates may be misleading. The results of morbidity studies, which are in progress, have to be awaited before drawing final conclusions.

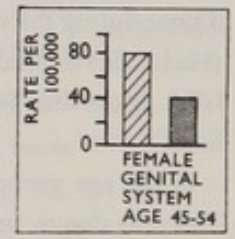
CANCER MORTALITY BY SITE AND ETHNIC GROUP (1950-1954)

AGE SPECIFIC RATES FOR
AGE GROUP 65 AND MORE

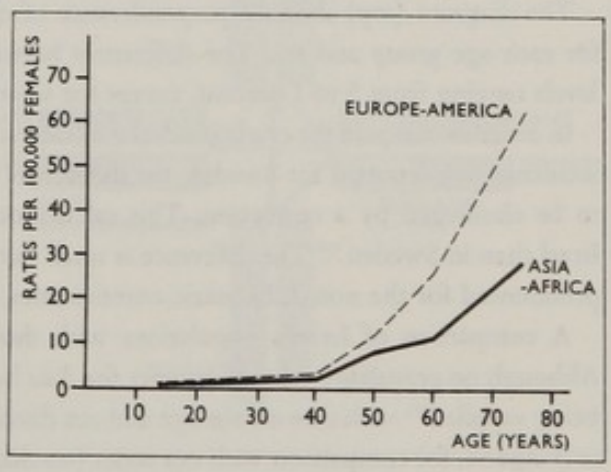


OCCIDENTALS (EUROPE-AMERICA)

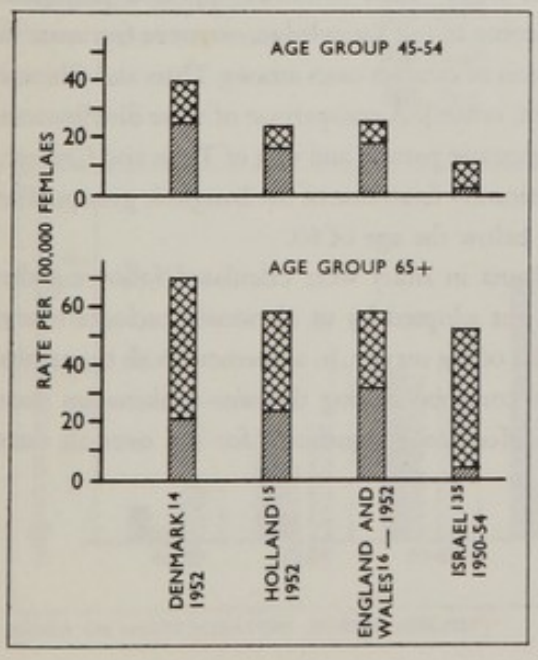
ORIENTALS (ASIA-AFRICA)



MORTALITY FROM CANCER OF CORPUS UTERI BY CONTINENT OF BIRTH AND AGE GROUP (1950-1954)



MORTALITY FROM CARCINOMA UTERI IN ISRAEL AND SOME EUROPEAN COUNTRIES



CORPUS

CERVIX

NOTE DIFFERENCES IN CERVIX-CORPUS RATIO

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For various juvenile types of cataract and glaucoma a genetic basis is clearly established; but there is only scanty information on the heritability of the senile forms of these diseases.[229, 87] As in the case of other chronic afflictions, geographic epidemiology may be expected to contribute to the clarification of the etiology of these eye diseases by uncovering environmental factors involved in their causation. Indeed, epidemiological studies have demonstrated quite recently[116] that certain poppy alkaloids may be responsible for a large proportion of glaucoma morbidity in some parts of India.

We have studied the incidence of senile cataract[117] and glaucoma[148] in the two main sectors of the Jewish population in Israel. Our material comprises all patients hospitalized for either of these conditions during the years 1956-57 in one of the four large ophthalmological departments of the country (Hadassah Hospital, Jerusalem; and the Government Hospital Rambam-Haifa, Tel-Hashomer, and Jaffa). More than 90 percent of all hospitalized ophthalmological patients of Israel are included in this series.

In the age groups 40 and over we registered 1130 cases of cataract in all (nuclear and cortical). Cataracts due to trauma or metabolic disturbances were not included. The incidence by age group, sex, and population sector was calculated, utilizing the official population statistics. For the purpose of this calculation the ethnic composition of the Israel-born population group was assumed to resemble that of the foreign-born.

The diagram (top) shows a preponderance of cataract among the non-Ashkenazic communities for each age group and sex. The differences between the two population sectors are significant at levels ranging from 5 to 1 percent, except for women aged 60 and over.

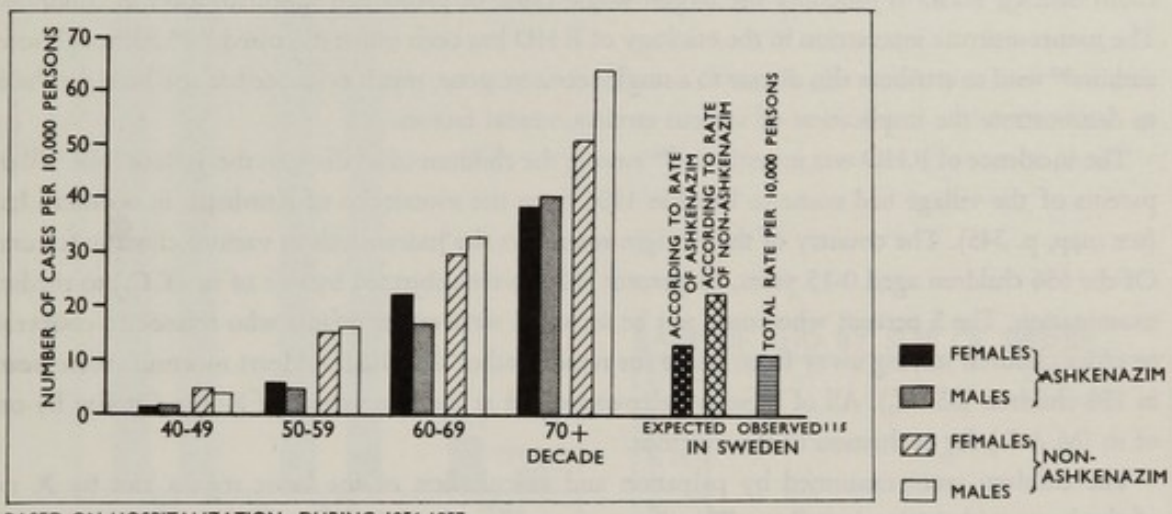
In order to compare the crude incidence of cataract in the two ethnic groups of Israel with the crude incidence rate reported for Sweden, the differences in the age stratification of these populations have to be eliminated by a correction. This calculation (top) shows that cataract is more common in Israel than in Sweden.[115] The difference is small but significant for Ashkenazic Jews. It is much more pronounced for the non-Ashkenazic communities.

A comparison of Israel's populations with those of other Asian countries appeared indicated. Although no prevalence rates of cataract for Asia have come to our knowledge, we were fortunate in being supplied[232] with data on the age and sex distribution of cataract cases among Thais and Chinese in Bangkok, for comparison with our series (see diagram, center). A comparison of these distributions by χ^2 tests indicates a resemblance between the non-Ashkenazic pattern and that of Thais and Chinese, whereas the distribution of Ashkenazic cases differs significantly from that of the Bangkok groups. The main difference lies in the scarcity of Ashkenazic cases below the age of 60.

The age- and sex-specific morbidity rates for glaucoma in Israel were calculated following the method outlined for cataract. The mode of ascertainment adopted by us obviously excludes many lighter cases which were not hospitalized during the years of the survey. In agreement with the results of previous authors[37] we found that glaucoma is more common among the non-Ashkenazim than among European Jews (see diagram, bottom). This difference is significant for the over-all rates though not for the age- and sex-specific rates.*

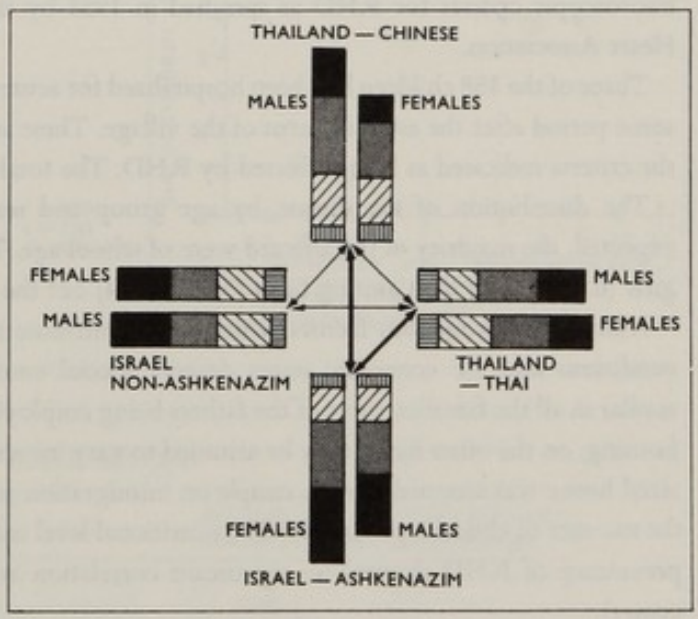
* The authors are greatly obliged to Miss M. Hagberg of the Swedish Institute, Stockholm, and the Swedish Committee on International Health Relations as well as to Dr. B. Subhamani, Ministry of Health, Thailand, for supplying valuable statistical data. Thanks are also due to the Records Officers of the Tel-Hashomer, Rambam, and Jaffa Government Hospitals for collecting the cases on which this study is based.

INCIDENCE OF SENILE CATARACT BY AGE AND SEX COMPARED WITH INCIDENCE IN SWEDEN[115]



BASED ON HOSPITALIZATION DURING 1956-1957

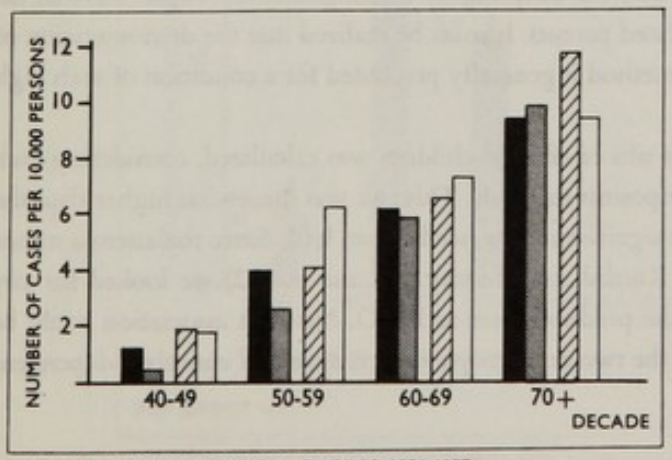
BREAK-UP OF CATARACT CASES BY AGE AND SEX IN ISRAEL AND IN THAILAND[232]



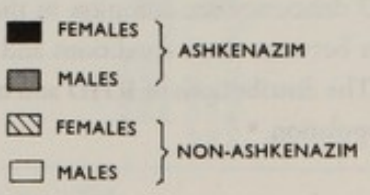
FOR EACH GROUP MALE AND FEMALE CASES OF ALL AGES ADD UP TO 100 PERCENT

DIFFERENCE
NOT SIGNIFICANT
HIGHLY SIGNIFICANT

AGE GROUPS
40-49
50-59
60-69
70+



AGE-SPECIFIC MORBIDITY RATES FOR GLAUCOMA IN ISRAEL



BASED ON HOSPITALIZATION DURING 1956-1957

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A HIGH PREVALENCE of rheumatic heart disease (RHD) among the children of Jerusalem and the neighboring areas of the Judean hills has been indicated by several investigators.[41, 134, 235] In the Jerusalem district, RHD is probably the largest single cause of prolonged hospitalization in childhood. The nature-nurture interaction in the etiology of RHD has been much discussed.[72, 231] Although some authors[262] tend to attribute this disease to a single recessive gene, much evidence has also been produced to demonstrate the implication of various environmental factors.

The incidence of RHD was investigated[64] among the children of a village in the Judean hills. All the parents of the village had come to Israel in 1951 from the mountains of Kurdistan in northern Iraq (see map, p. 345). The country of their origin resembles the Judean hills in various climatic features. Of the 656 children aged 0-15 years, 95 percent (620) were subjected by one of us (T.C.) to medical examination. The 5 percent who could not be included were either infants who refused to cooperate or older children staying away from home for reasons other than RHD. Heart murmurs were heard in 158 children (25.5%). All of these were re-examined at the heart clinic of Kupat-Cholim by one of us (M.A.S.) for evaluation of the murmur.

The children were examined by palpation and auscultation of the heart region and by X ray of the heart with barium swallow. The diagnosis was based on the generally accepted clinical and fluoroscopic criteria for RHD as specified in 1953 by the Criteria Committee of the New York Heart Association.

Three of the 158 children had been hospitalized for acute rheumatic fever prior to our survey during some period after the establishment of the village. These and another 34 children were recognized by the criteria indicated as being affected by RHD. The total number of affected was therefore 37.

The distribution of the disease by age group and sex is indicated in the histogram (top). As expected, the majority of the affected were of school age. The prevalence of RHD was higher among girls (6.76 ± 1.46) than among boys (5.25 ± 1.24) but the difference was not significant.

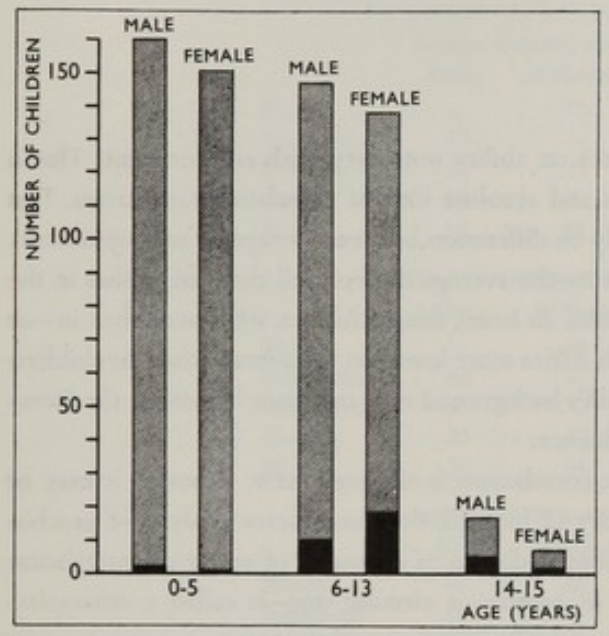
Among the exogenous factors which may contribute to the manifestation of RHD the housing conditions and the economic status deserve special consideration. Paternal occupations are fairly similar in all the families, most of the fathers being employed as laborers. The standard of living and of housing, on the other hand, may be assumed to vary inversely with the size of the family. A standard-sized home was assigned to each couple on immigration and crowding is therefore directly related to the number of children per family. The nutritional level may follow the same trend. Nevertheless, the prevalence of RHD showed no significant correlation with family size (see scatter diagram, right center).

The histogram (right bottom) indicates that the offspring of consanguineous couples showed no higher morbidity than the children of unrelated parents. It must be realized that the demonstration of recessive inheritance by the consanguinity method is generally precluded for a condition of such high prevalence.

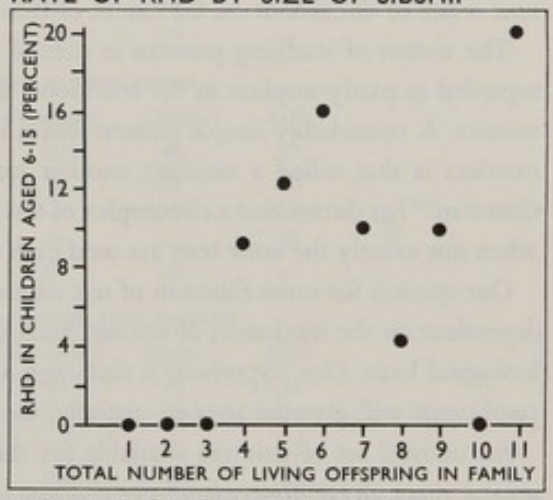
For the age group 6-15 years, the risk for sibs of affected children was calculated, considering each affected child as propositus (Weinberg's propositus method). This risk was somewhat higher than the general incidence in this age group, but not significantly so (see bottom left). Since thalassemia minor and G6PD deficiency are common in the Kurdish community (see also p. 272) we looked for any association between these conditions and the predisposition to RHD. No such association could be detected. The distributions of RHD and of the two erythrocyte defects appeared entirely independent in this population.*

* This research was supported by a grant from the Ford Foundation.

DISTRIBUTION OF RHD BY AGE AND SEX



RATE OF RHD BY SIZE OF SIBSHIP



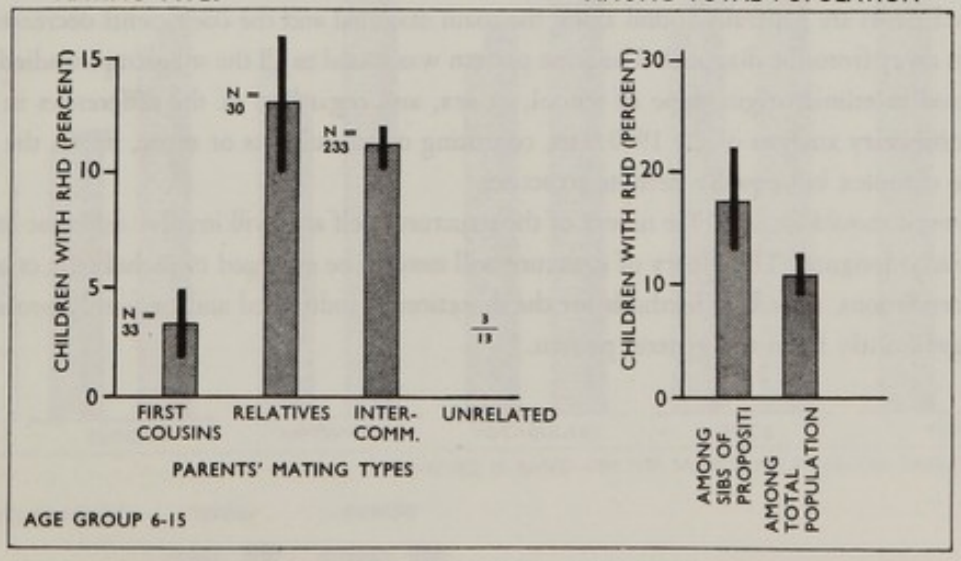
$r = 0.38$
$t = 1.23$
$p = 0.2—0.3$

PREVALENCE OF RHD IS NOT SIGNIFICANTLY CORRELATED WITH FAMILY SIZE (ECONOMIC STATUS)

RATE OF RHD

IN OFFSPRING OF VARIOUS MATING TYPES

AMONG SIBS OF AFFECTED AND AMONG TOTAL POPULATION



HEIGHTS OF BLACK BARS INDICATE ± 1 ST.E.

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IT IS WELL KNOWN that statistical features of scores on ability tests vary with environment. This is especially true of averages, and also of variances and absolute sizes of correlation coefficients. Past studies of human abilities have concentrated largely on differences between *averages* of subpopulations. In the United States, Negroes and Puerto Ricans on the average do less well than the whites in the same geographic area or of the same economic status. In Israel, schoolchildren who were born in—or whose parents came from—the Near East or North Africa score lower on the average than do children of European origin. Since it is known that the child's background may influence his scores, the literature is full of discussions on the extent of this influence.

The notion of studying patterns in mental test correlations is relatively new, although it may be regarded as partly implicit in the traditional theory of multiple-common-factor analysis of psychometrics. A remarkably simple pattern found in several dozens of examples of empirical correlation matrices is that called a *simplex;* another kind of pattern—a circular one—is called a *circumplex.* Guttman[114] has shown that a circumplex of test scores can be invariant with respect to age groups, even when not exactly the same tests are used each time.

Our quest is for some function of test scores that will not vary with environment or be essentially dependent on the mechanics of testing. Such a function, if it exists, could be hypothesized to have a biological basis. Our hypothesis is that even a higher order of function of the data than correlation coefficients will give the answer—namely, the *pattern* of intercorrelations.

An unusual set of data are available for this study, already on punchcards. For each of the past several years, all eighth-grade school children in Israel have taken a battery of tests especially compiled by the Ministry of Education. The pupils can be subclassified by sex, age, country of birth, origin of parents, length of stay in Israel, type of school, and average level of school achievement.

The table (top right) shows that a pattern does indeed exist among intercorrelations of scores on five subjects. Although average scores vary significantly between children of Yemenite and European origin and children born in or outside of Israel (see diagram, right), the relationship between the subjects follows a definite order for all groups of students. The pattern is an approximate simplex: the largest coefficients are generally found along the main diagonal and the coefficients decrease in size as one moves away from the diagonal. The same pattern was found in all the subgroups studied, whether they differed in ethnic origin, type of school, or sex, and regardless of the differences in their test scores. Preliminary analysis of the 1960 tests, consisting of ten subjects or more, shows the existence of a more complex but equally definite structure.

Future work should focus on the nature of the structure itself and will involve different batteries of tests especially designed. The theory of structure will need to be enlarged to include the crucial intrafamilial correlations, as well as methods for the detection of individual and/or family profiles which deviate significantly from the general pattern.*

* These studies were supported in part by grant M-5159(A) from the U.S. Department of Health, Education and Welfare.

INTERCORRELATIONS OF SCORES IN FIVE TEST SUBJECTS

FATHER, MOTHER, AND PUPIL BORN IN YEMEN

	Blocks	*Arithmetic*	*Vocabulary*	*Civics*	*Bible*
Blocks	—	.73	.65	.63	.53
Arithmetic	.73	—	.75	.65	.65
Vocabulary	.65	.75	—	.69	.69
Civics	.63	.65	.69	—	.81
Bible	.53	.65	.69	.85	—

FATHER AND MOTHER BORN IN YEMEN, PUPIL IN ISRAEL

	Blocks	*Arithmetic*	*Vocabulary*	*Civics*	*Bible*
Blocks	—	.63	.57	.33	.32
Arithmetic	.63	—	.72	.47	.54
Vocabulary	.57	.72	—	.52	.56
Civics	.33	.47	.52	—	.73
Bible	.32	.54	.56	.73	—

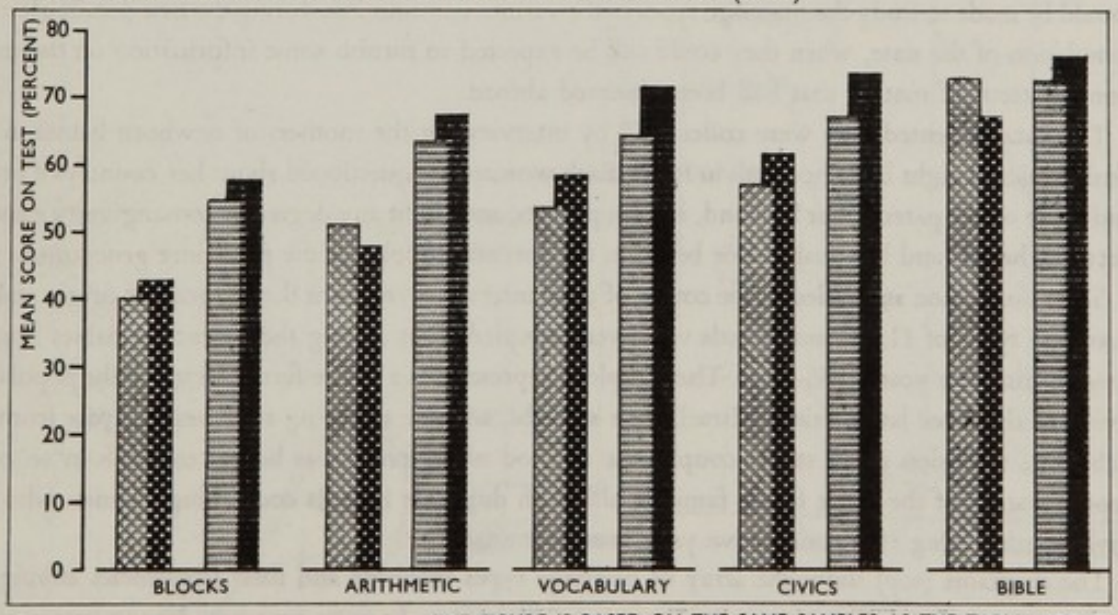
FATHER, MOTHER, AND PUPIL BORN IN EUROPE

	Blocks	*Arithmetic*	*Vocabulary*	*Civics*	*Bible*
Blocks	—	.69	.60	.46	.43
Arithmetic	.69	—	.74	.55	.55
Vocabulary	.60	.74	—	.38	.57
Civics	.46	.55	.38	—	.69
Bible	.43	.55	.57	.69	—

FATHER AND MOTHER BORN IN EUROPE, PUPIL IN ISRAEL

	Blocks	*Arithmetic*	*Vocabulary*	*Civics*	*Bible*
Blocks	—	.71	.57	.42	.34
Arithmetic	.71	—	.71	.52	.49
Vocabulary	.57	.71	—	.52	.52
Civics	.42	.52	.52	—	.62
Bible	.34	.49	.52	.62	—

SCORES ON EIGHTH GRADE STIPEND EXAMINATION (1955)



THE FIGURE IS BASED ON THE SAME SAMPLES AS THE TABLE (ABOVE)

PARENTS BORN IN: YEMEN EUROPE

PUPIL BORN IN: YEMEN ISRAEL EUROPE ISRAEL

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GENETIC DIFFERENTIATION among the Jewish communities is clearly reflected in the gene frequencies at many loci governing the polymorphisms on which the biochemical anthropologist (see pp. 254-278) bases his broad classifications. Similarly, the distribution of many of the rarer inherited disorders indicates a good deal of genetic heterogeneity among the Jewish tribes (see pp. 286-299).

The evidence for genetic differentiation among the Jews is unequivocal insofar as it derives from the study of simple Mendelian traits with complete penetrance. The differences in the susceptibility of the various communities to the common diseases of middle and old age (pp. 318-335) may in part be environmental rather than genetic. Much further analysis of these differences is required before they may be applied to a genetic characterization of the Jewish groups. The same is true of the morphological features with which the physical anthropologist is concerned. Pigmentation and skeletal characteristics are known to vary with certain environmental factors. Although an expansion of the scanty existing information on the physical anthropology of the Jews is highly desirable (see also pp. 282-285), this information will have to be interpreted with caution unless supported by parallel findings of the biochemical anthropologists.

A variety of factors may have been responsible for the genetic diversification of the Jewish communities. The most important among these agents were probably selection in different environments, gene flow, mutation, and the parameters of the various populations—in particular their size and breeding structure.

Inbreeding in small isolated groups may certainly be an important factor in promoting rapid evolutionary changes. No quantitative data on the breeding structure of the Jewish communities in centuries past are available to us. Even the mating systems of the Ashkenazic Jews have not been thoroughly studied, and the few available records[28] are based on small congregations which were probably not representative of European Jewry in general.

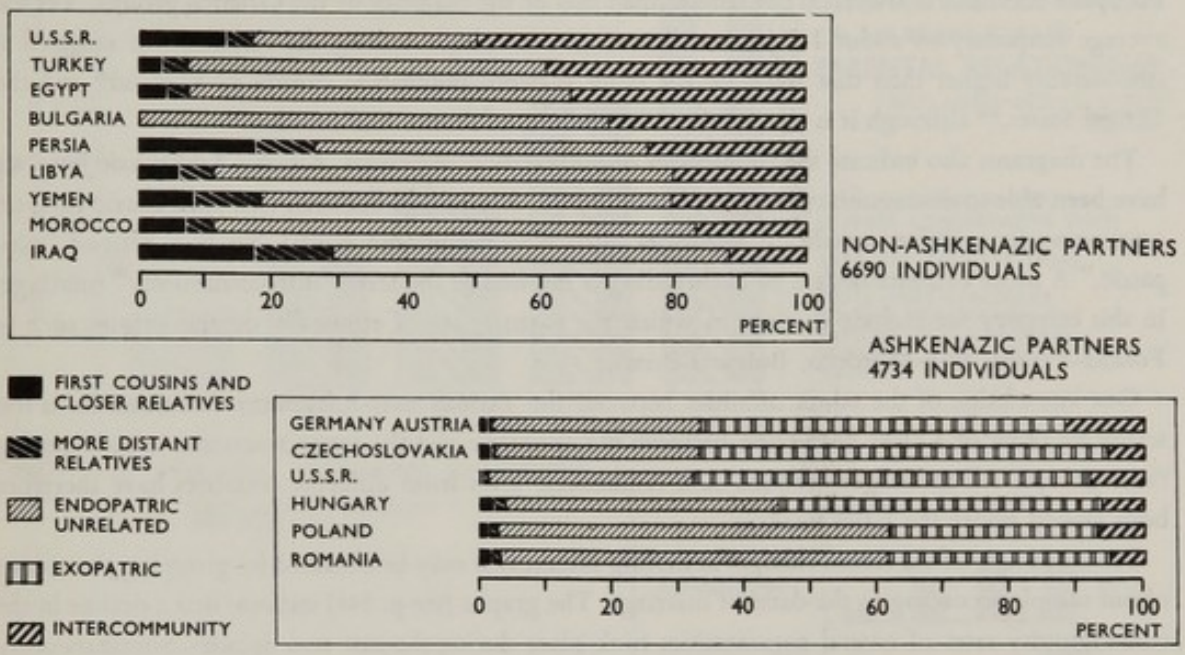
The integration of the Jewish communities into the developing society of the State of Israel will affect the traditional pattern of life in each immigrant group. The mating systems that were accepted in the diaspora cannot be expected to survive this social revolution. We felt, therefore, that an effort should be made to study the marriage types in the various communities during the first decade after the foundation of the state, when they could still be expected to furnish some information on the traditional pattern of mating that had been observed abroad.

The data presented here were collected[103] by interviewing the mothers of newborn babies in the birth clinics of eight large hospitals in Israel. Each woman was questioned about her country of origin and those of her parents, her husband, and his parents, and about any degree of consanguinity existing between herself and her husband or between the parental couples of the preceding generation.

The information assembled in the course of these interviews concerns the geographic origin and the marriage types of 11,424 individuals who were sampled from among the parents of babies born in Israel during the years 1955-1957. The sample is representative of the fertile sector of the population living in the three large cities of Israel, their suburbs, and the adjoining rural areas. Apart from the deliberate exclusion of all sterile couples the method of sampling was bound to result in an overrepresentation of the more fertile families, although duplicate records concerning women who had given birth during two consecutive years were eliminated.

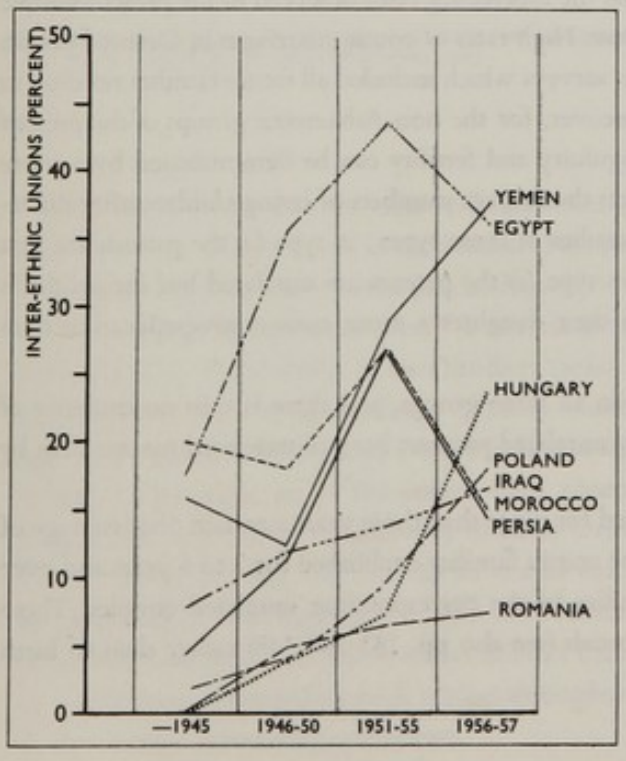
The diagrams (top) show the array of marriage types recorded and their frequencies among the various communities. Consanguineous marriages are seen to be very common among many of the non-Ashkenazic communities, in particular among those from Iraq, Persia, Yemen, and the Asiatic

DISTRIBUTION OF MARRIAGE TYPES AMONG PARENTS OF BABIES BORN 1955-57

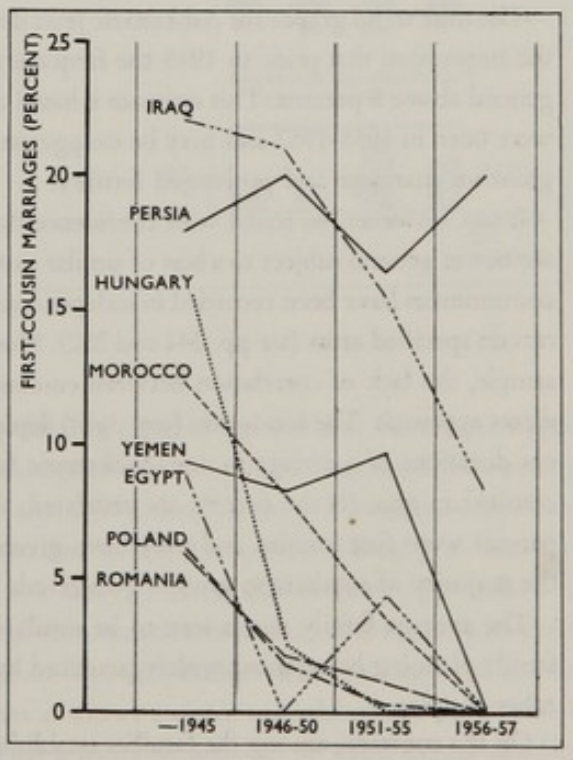


TIME TRENDS IN MARRIAGE SYSTEMS

RATE OF INTER-ETHNIC UNIONS



RATE OF FIRST-COUSIN MARRIAGES



NOTE: DECLINE IN CONSANGUINITY AND RISING FREQUENCY OF INTER-ETHNIC UNIONS CONTRIBUTE JOINTLY TO HETEROZYGOSITY OF COMING GENERATION

part of the U.S.S.R. The consanguinity rate of the Ashkenazic Jews who immigrated from various European countries is lower, on the whole, than that of the majority of the Oriental groups. Yet the average frequency of about 1.5 percent first-cousin marriages among the Ashkenazim sampled is considerably higher than that recorded for large Western population groups in England[28] and the United States,[264] although it is exceeded in certain areas of France and Sweden.[38]

The diagrams also indicate the frequencies of outbreeding marriages. Among Ashkenazic Jews we have been able to distinguish two types of such unions. A marriage between two Ashkenazic partners originating from different political territories, such as Germany and Russia, has been termed "exopatric." A more extreme degree of outbreeding is implied in the term "intercommunity" marriage. In this category we include matings in which the partners are of ethnically diverse origins such as Poland-Yemen, Iraq-Morocco, Bulgaria-Persia.

Our knowledge of the ethnic affinities between the various non-Ashkenazic communities is too scanty to allow of a clear distinction between the exopatric and the intercommunity unions among these groups. All marriages between non-Ashkenazic Jews from different countries have therefore been classed under the latter heading.

Some estimate of the recent changes in mating preferences may be obtained by grouping the unions of our sample according to the dates of marriage. The graphs (see p. 341) indicate that a decline in the consanguinity rates of several communities took place during the past two decades. Simultaneously there was an increase in the frequency of the interethnic marriage. In contradistinction to the other groups, the mating types of Persian Jews present a relatively static pattern. This may be due to the sparse representation of this community in Israel or to sampling errors.

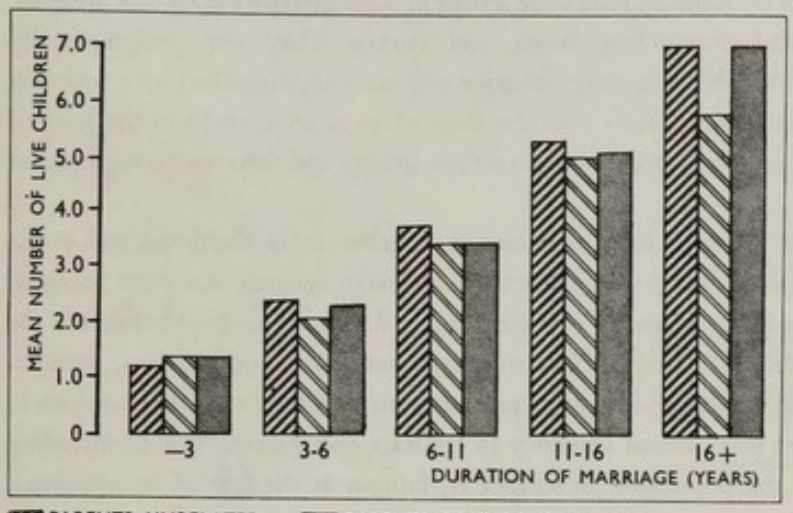
The time trend graphs for Ashkenazic Jews should be interpreted with similar caution. They convey the impression that prior to 1945 the frequency of first-cousin marriages in this community was in general above 5 percent. This estimate is based on a limited number of older couples to whom babies were born in 1955-1957 and may be exaggerated owing to the probable association between consanguineous marriage and prolonged fertility.

It can, however, be stated with confidence that the inbreeding rates observed in the present sample are not in general subject to a bias of similar extent. High rates of cousin marriages in Oriental Jewish communities have been recorded in independent surveys which included all fertile families residing in certain specified areas (see pp. 344 and 352). Moreover, for the non-Ashkenazic groups of the present sample, the lack of correlation between consanguinity and fertility can be demonstrated by a more direct approach. The histogram (top right) depicts the average numbers of living children after different durations of marriage in non-Ashkenazic families of three types: in type (*a*) the parents are first cousins; in type (*b*) the parents are unrelated; in type (*c*) the parents are unrelated but the mother's parents were first cousins and may have given their daughter a more conservative education than the majority of mothers in group (*b*) received.

The average family size is seen to be similar in all three groups, and there is thus no evidence of family planning being more widely practiced by unrelated partners born to unrelated parents than by other couples.

On the contrary, among the families established for more than three years a certain disadvantage of the cousin families becomes apparent. Indeed, the cousin families established for 3 to 6 years and over 16 years are significantly smaller than the families of the corresponding unrelated couples. These differences appear to be due to viability differentials (see also pp. 183 and 348) rather than to birth control. *

* This research was supported by a grant from the Ford Foundation.

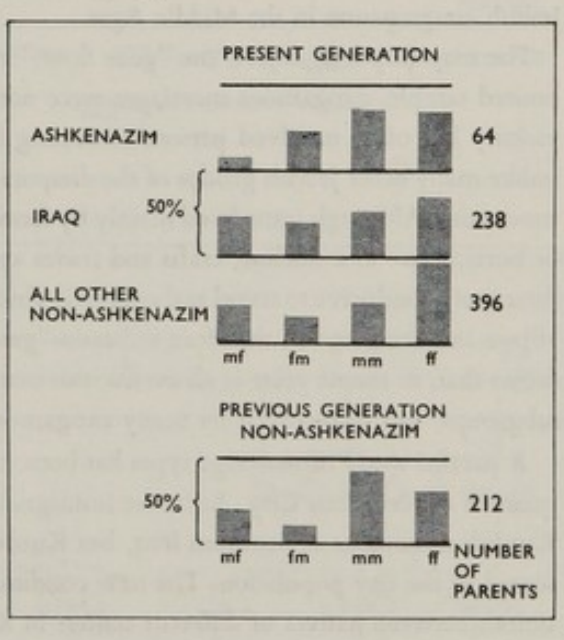


AVERAGE NUMBER OF LIVE OFFSPRING BY DURATION OF MARRIAGE AND PARENTAL RELATIONSHIP

(NON-ASHKENAZIM)

CONSANGUINEOUS COUPLES, IF MORE CONSERVATIVE THAN UNRELATED PARENTS, WOULD BE EXPECTED TO HAVE MORE CHILDREN.
NOTE THAT CONTRARY TO THIS EXPECTATION THE FAMILIES OF COUSINS ARE SOMEWHAT SMALLER ON THE AVERAGE.

PARENTS UNRELATED
PARENTS FIRST COUSINS
MOTHER'S PARENTS FIRST COUSINS



RELATIVE FREQUENCIES OF FOUR CLASSES OF COUSIN MARRIAGES

UNIONS BETWEEN CHILDREN OF LIKE-SEXED SIBS (mm + ff) ARE PREFERRED IN MANY JEWISH COMMUNITIES

mf: DAUGHTER OF BROTHER WITH SON OF SISTER
fm: DAUGHTER OF SISTER WITH SON OF BROTHER
mm: DAUGHTER AND SON OF BROTHERS
ff: DAUGHTER AND SON OF SISTERS

THE GRANDPARENTAL GENERATION FAVORED THE MARRIAGE BETWEEN CHILDREN OF TWO BROTHERS (mm)

It is well known[220] that the relative frequencies of the four possible types of first-cousin marriages may shed some light on the social motivation of the consanguineous mating. The diagram (right center) shows that the marriage between the children of two sisters (ff), which is the preferred type of cousin union in several European samples,[220] is not more common among European and Iraqi Jews than the match between the children of two brothers (mm). It is also of interest that the latter type, which is held in high esteem by the tradition of many Moslem communities, is no longer the most prevalent among the younger immigrants from Moslem countries. The distribution of the four types of unions among the grandparents of the present baby generation shows a closer resemblance to the Moslem pattern (see bottom row of diagram). In many Oriental Jewish communities no social stigma attaches to the cousin marriage and the rate of cousin marriages shows no correlation with the size of the congregation. These communities may have maintained high consanguinity rates for many generations. Yet, although tradition tended to stabilize the rate of inbreeding, the expansions and contractions to which these communities were subject throughout historic times must have had their repercussions in the average inbreeding coefficients.

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BEFORE THEIR IMMIGRATION to Israel the Kurdish Jews were settled in the mountain ranges of Kurdistan, which are today politically divided among Iraq, Persia, and Turkey. They were geographically isolated from the major Jewish centers of these three countries and were distinguished by a tradition and a language ("Targum") of their own.[32] They consider themselves as set apart from the Jews of Teheran, Baghdad, and Istanbul and refer to unions between these groups and their own congregation as "Intercommunity Marriages."

We have visited all the families in a settlement of recent immigrants from Kurdistan and in the course of prolonged interviews have tried to reconstruct the marriage systems that were accepted among this group while still abroad. The majority of these families derived from four hamlets in the Kurdish mountains of northern Iraq. The frequency of marriages between blood relatives, between unrelated partners born in the same hamlet, and between persons born in different hamlets is shown in the diagram (top right). The most pronounced tendency to contract endogamous unions including cousin marriages is displayed by the population of hamlet A, famous as the seat of an important Jewish congregation in the Middle Ages.

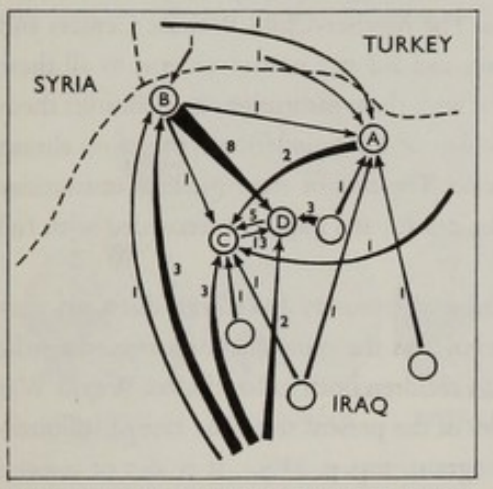
The map (top left) depicts the "gene flow," recorded in our data. It can be seen that, even in this limited sample, exogamous marriages were not restricted to the four hamlets and their immediate vicinity but often involved persons stemming from distant towns and villages. The Kurdish Jews, unlike many other Jewish groups of the diaspora, were bound by strong ties to the soil of their native mountains. Although some lived mainly by farming and many others practiced small-scale agriculture or horticulture as a sideline, crafts and trades appear to have been the predominant professions, and these were conducive to travel and courtship abroad. As a rule, the young couple settled in the groom's village and the diagram therefore indicates "gene flow" as a migration of brides. Thus our evidence shows that, in recent years at all events, this community, far from being split up into strictly isolated subgroups, was interwoven by many exogamous unions.

A parallel study of marriage types has been conducted among the Kurdish Jews inhabiting several quarters of Jerusalem City. As in the immigrant village, the majority of this group derive from the Kurdish mountains of northern Iraq, but Kurdish Jews from Turkey and from Persia are also represented in the city population. The new conditions and contacts in the city greatly favor exogamous unions between natives of different centers in Kurdistan. The map (bottom left) indicates this "gene flow," which tends to merge the populations of different Kurdish centers.

The Kurdish Jews of Jerusalem have also contracted numerous marriage unions with members of other Jewish communities (diagram, center, p. 347) and the interethnic union is today as popular as the consanguineous marriage (diagram, top right, p. 347).

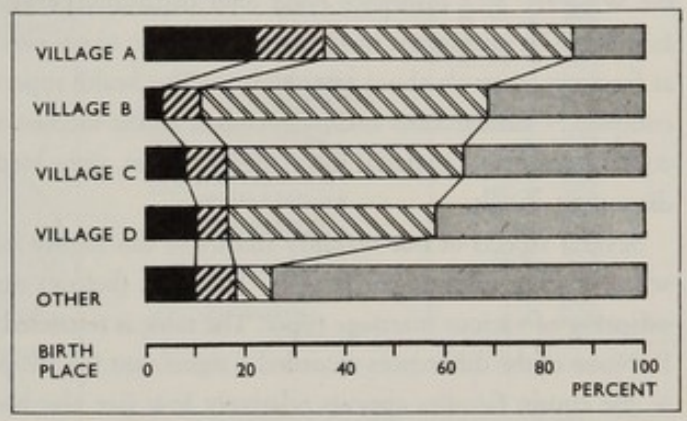
We have tried to determine whether certain clans persist in favoring marriages between blood relatives, while other less conservative kinships prefer the exogamous union. We have found no evidence of such familial tendencies to one or the other type of mating. The diagram (top left, p. 347) shows the frequencies of various marriage types among the parents of today's fertile couples. If the daughter's choice was influenced by her parents' marriage type, consanguineous unions should be more frequent among parents of women who have married first cousins than among those who contracted an interethnic union. No such correlation is reflected in the data. The occurrence of consanguineous and interethnic unions in consecutive generations and in collateral families of the same kinship is also shown in the pedigrees (center and bottom, p. 347). Unfortunately, no similar information is available for earlier generations. It is plausible that in former days some clans may have been more mobile than others, and more inclined to seek exogamous unions.

GENE FLOW AMONG KURDISH JEWS IN NORTHERN IRAQ

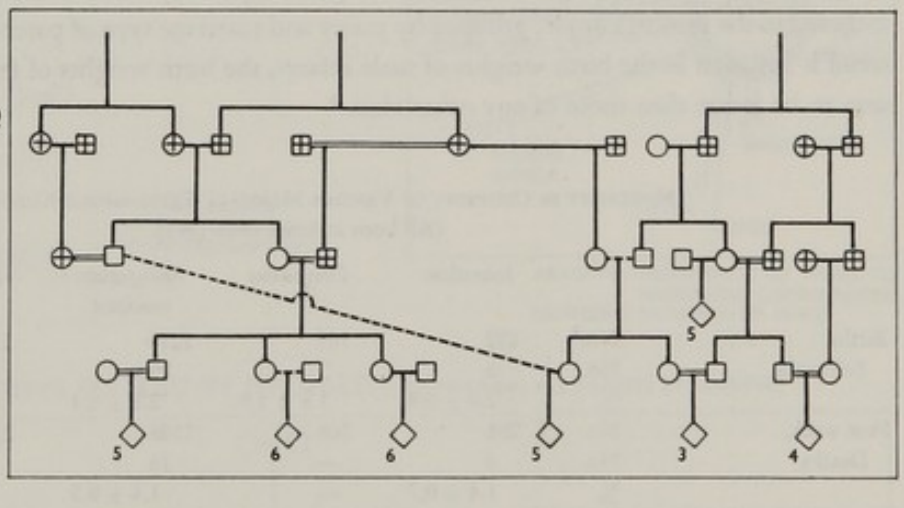


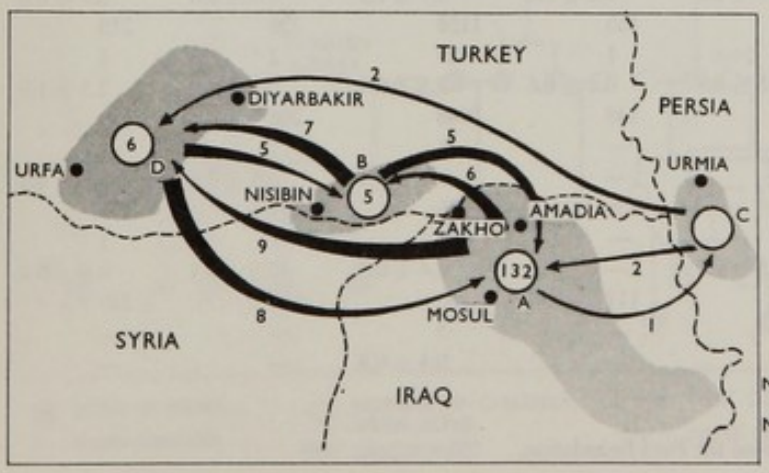
A B C D: FOUR VILLAGES WITH LARGE JEWISH CONGREGATIONS
ARROWS: MIGRATIONS OF BRIDES TO VILLAGES OF GROOMS
NUMBERS NEXT TO ARROWS: NUMBERS OF SUCH MIGRATIONS AMONG 218 COUPLES INTERVIEWED

DISTRIBUTION OF MARRIAGE TYPES AMONG KURDISH JEWS IN NORTHERN IRAQ



LARGE CLAN FROM VILLAGE A IN NORTHERN IRAQ





GENE FLOW AMONG KURDISH JEWS FROM DIFFERENT CENTERS IN KURDISTAN

BASED ON 188 COUPLES MARRIED IN ISRAEL AND SETTLED IN JERUSALEM

NUMBERS IN CIRCLES: ENDOGAMOUS WIVES
NUMBERS NEXT TO ARROWS: EXOGAMOUS WIVES

The present-day population of Kurdish Jews, with its wide array of marriage types, is easily amenable to viability studies, especially since endogamous and exogamous couples often live in the same neighborhood and under similar economic conditions. The Mother-Child Welfare Centers and the Workers' Sick Insurance Fund offer medical supervision and aid at a minimum cost to all these families. The immigrant mother quickly learns to cooperate with these institutions and consults them at frequent intervals about her children. The health supervision of this population is therefore almost completely standardized and independent of the income scale. The files of these medical institutions contain invaluable material for viability studies, since births, deaths, and illness are recorded with full diagnostic details.

Several aspects of our viability studies in this highly inbred community have been discussed elsewhere in this volume (see p. 183). The table (below) summarizes the mortality data regarding the offspring of various marriage types. The table is restricted to children born in Israel after World War II. None of the differences recorded is significant for samples of the present size. The rate of stillbirths in the cousin families appears relatively low (see also histogram, top, p. 349). It is also of interest that the incidence of malformations in cousin children, though higher than in the unrelated endogamous class, is closely matched in the offspring of interethnic couples (see histogram, p. 348).

Apart from increasing the risk of homozygosity for lethal and deleterious genes, consanguinity is expected to produce an "inbreeding depression" of various quantitative characteristics, such as height, weight, and possibly intelligence.[175,225] The diagrams (p. 348) indicate the birth weights of children included in the present sample, grouped by parity and marriage type of parents. Though no consistent trend is apparent in the birth weights of male infants, the birth weights of female cousin children are seen to be lower than those of any other class.*

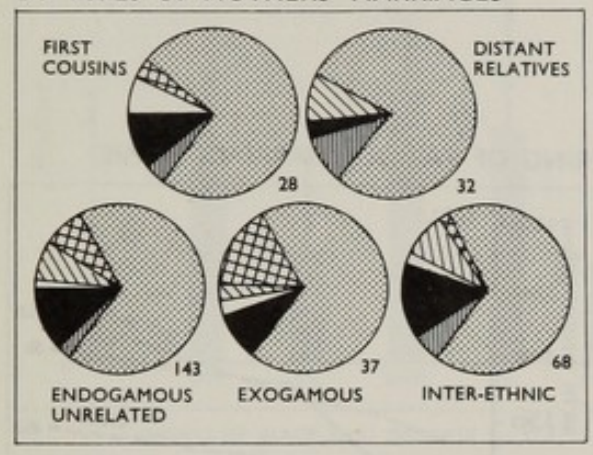
MORTALITY IN OFFSPRING OF VARIOUS MARRIAGE TYPES AMONG KURDISH JEWS
(All born in Israel 1945-1961)

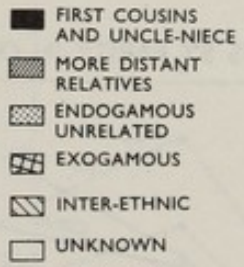
		Interethnic	*Exogamous*	*Endogamous unrelated*	*Relatives*	*First cousins*
Births,	No.†	292	169	1210	235	223
Stillbirths,	No.	6	3	25	4	3
	%	2.0 ± 0.8	1.8 ± 1.0	2.1 ± 0.4	1.7 ± 0.8	1.3 ± 0.7
First week,	No.	286	166	1185	231	220
Deaths,	No.	4	—	16	1	3
	%	1.4 ± 0.7	—	1.4 ± 0.3	0.4 ± 0.4	1.4 ± 0.8
Second to fourth week,	No.	282	166	1169	230	217
Deaths,	No.	2	1	11	2	2
	%	0.7 ± 0.5	0.6 ± 0.6	0.9 ± 0.3	0.9 ± 0.6	0.9 ± 0.6
Second to twelfth month,	No.	280	165	1158	228	215
Deaths,	No.	7	1	29	2	5
	%	2.5 ± 0.9	0.6 ± 0.6	2.5 ± 0.5	0.9 ± 0.6	2.3 ± 1.0
Second year,	No.	249	149	1048	208	194
Deaths,	No.	—	—	1	1	1
	%	—	—	0.1 ± 0.1	0.5 ± 0.5	0.5 ± 0.5
Third year,	No.	207	136	926	190	175
Deaths,	No.	1	—	4	1	1
	%	0.5 ± 0.5	—	0.4 ± 0.2	0.5 ± 0.5	0.6 ± 0.6
Fourth year,	No.	168	117	800	166	149
Deaths,	No.	—	—	3	—	—
	%	—	—	0.4 ± 0.2	—	—

† Twin births counted as two births.

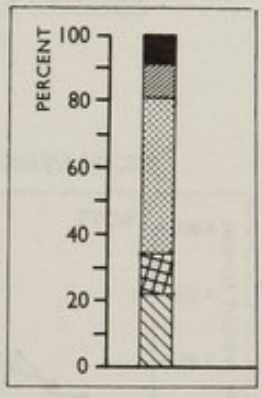
* This research was supported by a grant from the Ford Foundation.

DISTRIBUTION OF MARRIAGE TYPES AMONG PARENTS OF TODAY'S MOTHERS BY TYPES OF MOTHERS' MARRIAGES

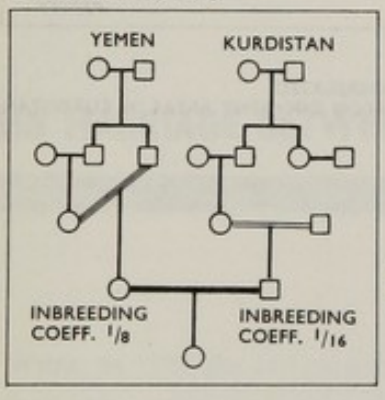


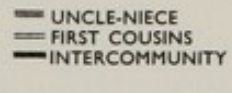


DISTRIBUTION OF MARRIAGE TYPES

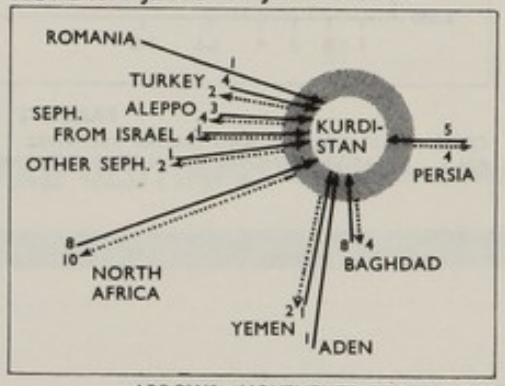


INTER-ETHNIC PARTNERS WITH HIGH COEFFICIENT OF INBREEDING



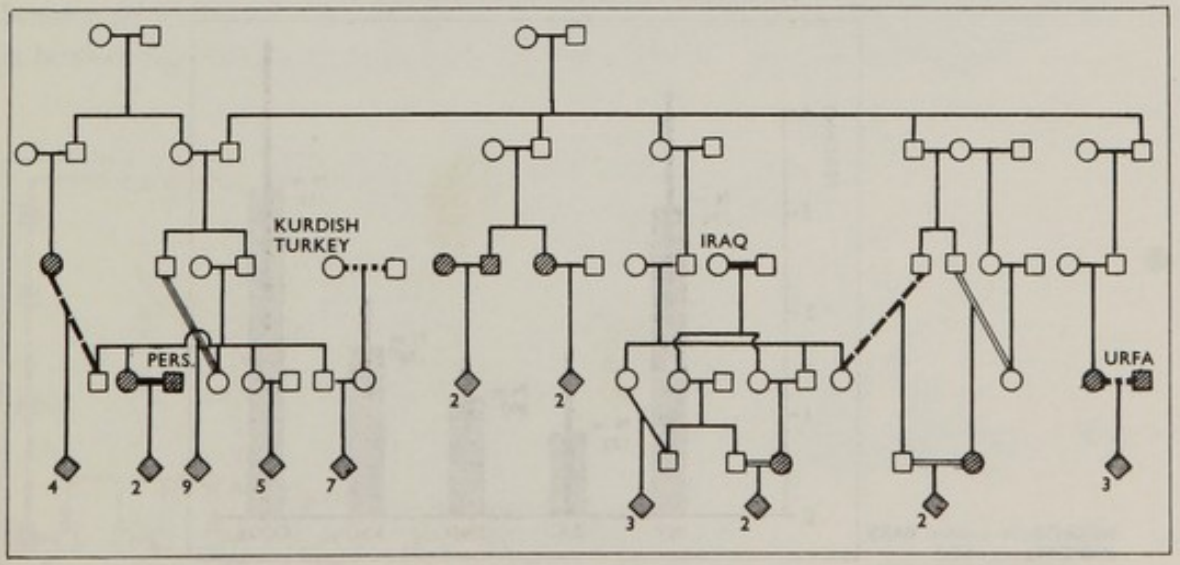


TYPES OF INTER-COMMUNITY MARRIAGES CONTRACTED BY KURDISH JEWS IN JERUSALEM



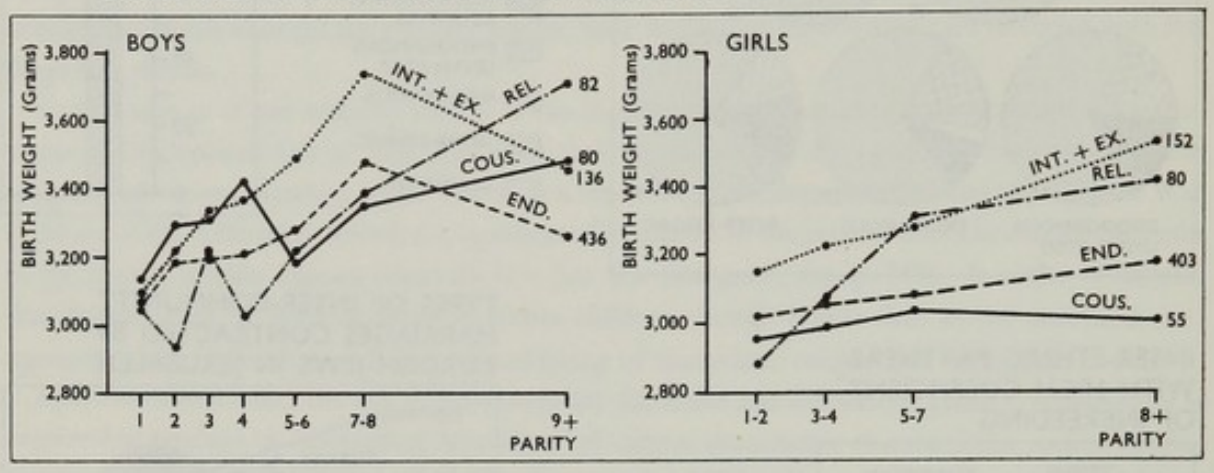
ARROWS: MOVEMENTS OF WIVES TO HUSBANDS' COMMUNITIES
NUMBERS: NUMBERS OF WIVES

CLAN OF KURDISH JEWS SETTLED IN JERUSALEM (COMPRISING ALL CLASSES OF UNIONS)



BORN IN ISRAEL
BORN ABROAD
NUMBER OF CHILDREN BORN ALIVE
UNCLE-NIECE
FIRST COUSINS
MORE DISTANT RELATIVES
EXOGAMOUS
INTER-ETHNIC

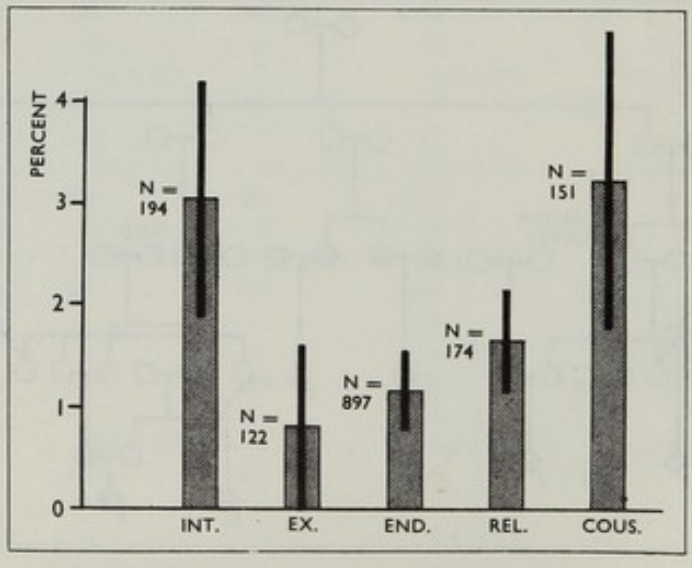
BIRTH WEIGHTS BY PARITY IN OFFSPRING OF VARIOUS MARRIAGE TYPES



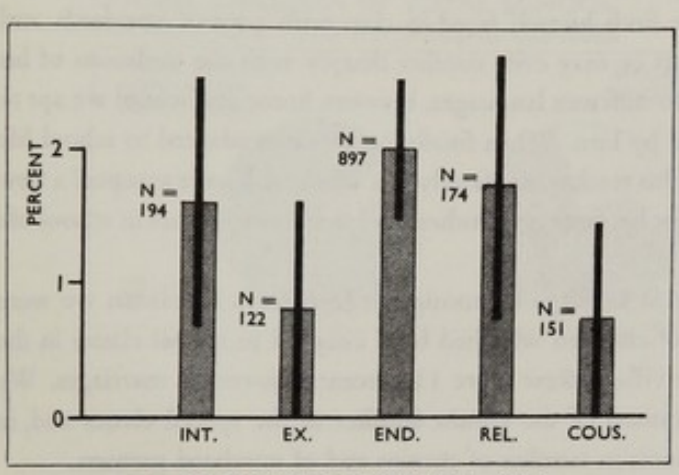
PARENTS' MARRIAGE TYPE

COUS.: FIRST COUSINS AND CLOSER RELATIVES
REL.: RELATIVES REMOTER THAN FIRST COUSINS
END.: ENDOGAMOUS UNRELATED
EX.: EXOGAMOUS — FROM DIFFERENT AREAS IN KURDISTAN
INT.: INTER-ETHNIC

INCIDENCE OF MAJOR MALFORMATIONS IN STILLBIRTHS AND LIVE BIRTHS



HEIGHTS OF BLACK BARS INDICATE: ±1 ST.E.



HEIGHTS OF BLACK BARS INDICATE ±1 ST.E.

INCIDENCE OF STILLBIRTHS IN OFFSPRING OF VARIOUS MARRIAGE TYPES
(BASED ON BIRTHS IN ISRAEL 1945—1960)

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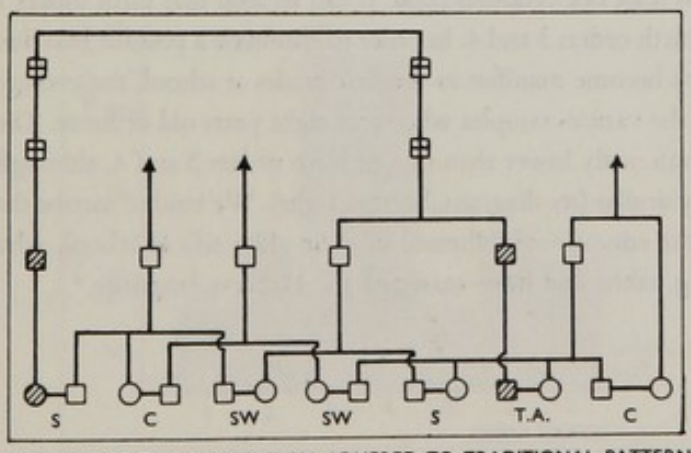
COUSIN MARRIAGE BETWEEN NEWCOMERS AND OLDTIMERS

D. Feitelson

When, in 1951, the vast majority of Kurdish Jews who had been left in Iraq immigrated to Israel, they were welcomed kindly by members of their kinships who had entered Palestine during the 'twenties and 'thirties of the present century. The family reunions resulted in cousin marriages between old residents and new immigrants. The pedigree shows a large clan whose members arrived in Israel during different periods and who are now settled in various parts of Jerusalem.



MEMBERS OF THIS LARGE CLAN ADHERED TO TRADITIONAL PATTERN OF CHOOSING PARTNER WITHIN KIN GROUP — DATE OF IMMIGRATION FORMED NO BARRIER

COUPLE'S DOMICILE:
C: CENTER
S: SOUTHERN SUBURB
SW: SOUTHWESTERN SUBURB } OF JERUSALEM
T.A.: SUBURB OF TEL-AVIV

□ NEW IMMIGRANT
▨ OLD SETTLER
⊞ DIED ABROAD
↑ RELATED TO SAME KINSHIP

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THE INTEGRATION of the immigrant family into the cultural pattern of a new country may involve acute hardship for the child at school. He finds himself faced in class with a set of standards and demands that are meaningless to his parents or may even conflict sharply with the traditions of his home. The messages he carries, often in two different languages, between home and school are apt to arouse anger, however faithfully translated by him. When finally he becomes adapted to school life and begins to comply with the demands of his teacher, the family as a whole will have accepted a new set of values. He will have paved the way for his younger brothers and sisters whose start in school life will be happier than was his own.

In the course of a consanguinity survey in a village of immigrant Jews from Kurdistan we were struck by the relatively large proportion of children who had been assigned to special classes in the village school. Among the parents of the village there were 13 percent first-cousin marriages. We decided to investigate the relative contribution of the cousin families to the special classes and, in addition, to compare the school achievements in families of cousins and of unrelated partners.

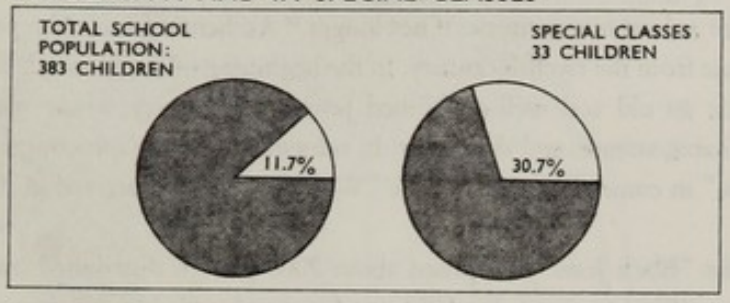
An intelligence test was administered[102] to the 38 cousin children attending the school and to a control group of 47 children of unrelated parents. The control families were selected to match the cousin families in the age distribution of the children. In order to reveal a possible familial incidence of mental retardation, the same test was also given to 32 of the 33 children attending the special classes and to 51 of their 57 sibs. The test was mainly verbal (Wechsler verbal scale) since other investigators[187, 263] in Israeli schools had demonstrated that nonverbal tests are far from culture-free.

The relative contribution of the cousin families to the classes of the retarded was significantly larger than their representation in the general school population (see diagram, top right). The cousin children did not differ significantly in their mean I.Q. (77.1 ± 1.7) from the control group (80.9 ± 1.5; $t = 1.71$; $d.f. = 83$, $p \sim 0.1$) but their lower scores in each of seven subtests (see figure, center) give a nonparametric indication of a significant difference. The cousin parents resembled the control couples in absolute age, age differential, occupation, and standard of living. It is, however, possible that apart from "inbreeding depression" a stricter adherence to traditional patterns of life in the cousin families interferes with the adaptation of their children to the Israeli school.

The mean scores of the pupils in special classes, of their sibs, and of the control group are shown in the histogram (center). The sibs of the retarded did slightly better than the control, though the difference was not significant. Although the sample may be too small to furnish information on the *heritability* of mental retardation, it does indicate the importance of an *environmental* influence on the development of mental ability. The histogram (bottom left) shows the average I.Q. scores for different birth ranks in the sibships with at least one retarded child. It can be seen that birth orders 1 and 2 rank much lower in their I.Q. than birth orders 3 and 4. In order to eliminate a possible bias due to the fact that mental retardation may not become manifest in the first grades at school, the average I.Q. was also calculated for all children of the various samples who were eight years old or more. The I.Q. of birth orders 1 and 2 was again significantly lower than that of birth orders 3 and 4, although the average age of both groups was closely similar (see diagram, bottom right). We tend to ascribe the advantage of the higher birth-orders to the educational influence of their older sibs at school, who have acquired certain elementary learning habits and have mastered the Hebrew language.*

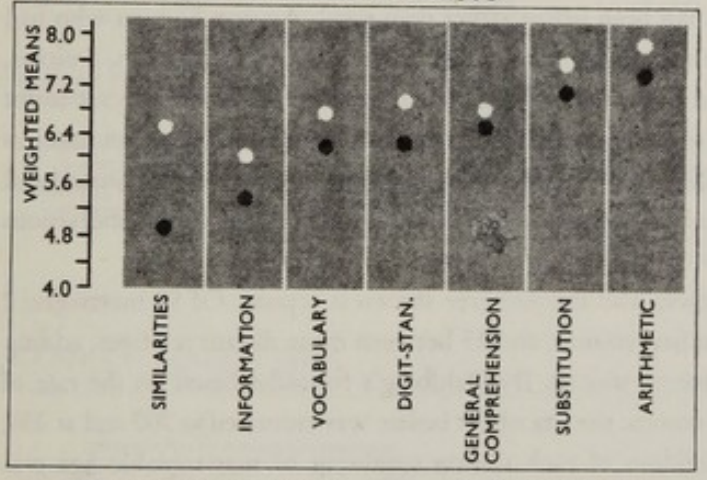
* This research was supported by a grant from the Ford Foundation.

COUSIN CHILDREN IN TOTAL SCHOOL POPULATION AND IN SPECIAL CLASSES



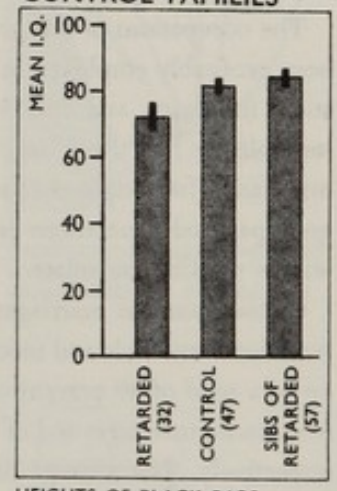
$\chi^2 = 10.84$ df. = 1 $p < .001$

SCORES OF COUSIN CHILDREN AND OF CONTROLS IN SEVEN SUBTESTS



(WECHSLER VERBAL SCALE)

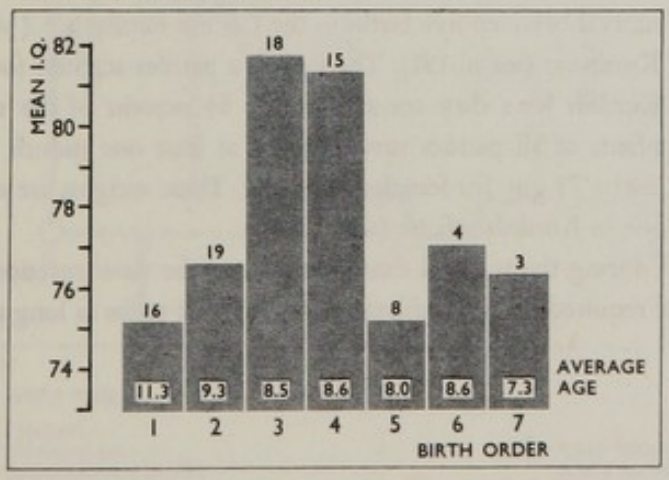
MEAN I. Q. SCORES IN SIBSHIPS OF RETARDED CHILDREN AND IN CONTROL FAMILIES



HEIGHTS OF BLACK BARS INDICATE ±1 ST.E.

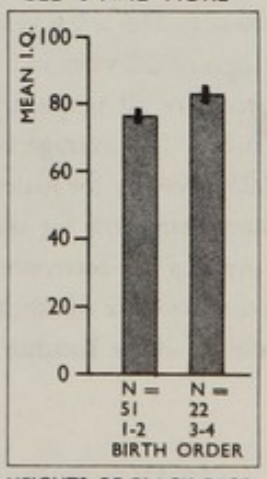
MEAN I.Q. BY BIRTH ORDER

A: IN SIBSHIPS WITH ONE RETARDED CHILD OR MORE



NUMBERS ABOVE BARS: NUMBER TESTED

B: OF ALL CHILDREN AGED 8 AND MORE



HEIGHTS OF BLACK BARS INDICATE ±1 ST.E.

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THE JEWS FROM COCHIN have attracted great interest,[79, 204, 267] both for being a very small and closely knit group and for their dark skin pigmentation. This congregation must have been settled in Cochin, on the Malabar Coast of India, for at least nine centuries if not longer.[86] Authentic travelers' reports on the Jews of the Malabar Coast date from the twelfth century. In the beginning of the sixteenth century the Portuguese found in Cochin an old and well-established Jewish community whose members resembled the native Indians in habit, stature, and skin color. In subsequent reports this congregation is referred to as the "Black Jews," in contradistinction to the "White Jews," who arrived in the area much later.

In 1954, the community of the "Black Jews" comprised about 2000 persons distributed over five small towns and villages. Of these, 1700 immigrated in 1954 into Israel and settled in different parts of the country. All of the 70-odd "White Jews" are reported to have remained in India.

In 1958 we studied the Cochin Jews settled in the village M. in the Jerusalem Corridor. After consulting the files of the Mother-Child Welfare Center, we visited and interviewed the 61 families of the village and examined most of their children.

The occupations of this group abroad had been urban rather than rural. Among 53 men who had been profitably employed in India, there were 29 merchants and traders, 9 factory workers, 5 clerks, and 5 fishermen, and only 5 had pursued other occupations. Since trading favors mobility, it is not surprising to find that a large proportion of the marriages in Cochin were concluded between partners originating from different hamlets and villages. The marriage movements for the present parental and grandparental generations (see maps) lead us to assume that there were no rigid local subdivisions within the Cochin isolate.

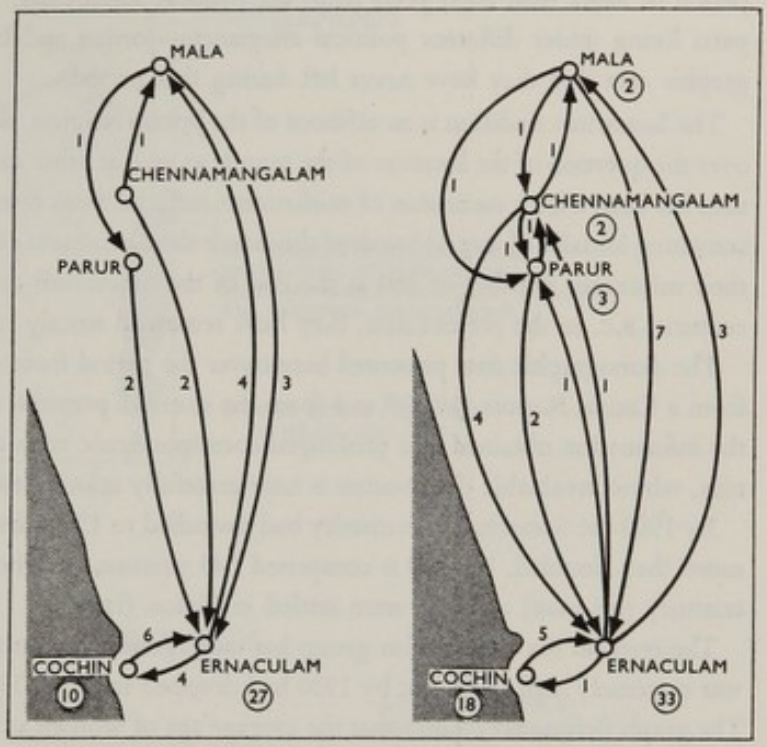
Consanguineous marriages were common, and the pedigree shown is typical. Of 59 marriages, 2 were between uncle and niece, 7 between first cousins, and 15 between more distant relatives, adding up to a total of 40 percent of consanguineous unions. By Dahlberg's formulas based on the rate of first-cousin marriages and of uncle-niece unions, the size of the isolate was estimated at 202 and at 235, respectively. The average number of children of each sibship surviving to marriageable age was assumed to be 4, as actually found in the present parent generation. The close agreement between the two estimates is rather exceptional.[96, 103, 174] Moreover, it is plausible that the fraction of the population that was eligible for marriage at any time comprised about 10 percent of the total. It therefore appears that in this community cousin marriages were indeed dictated by lack of choice rather than by tradition.

The mean age at marriage of 45 men was 24.2 ± 0.8 years, whereas the mean age of their 45 brides was only 17.6 ± 0.6 years. The average interval between live births in the Cochin family is 3.2 years as against 2.2 years in immigrants from Kurdistan (see p. 191). The first five parities account for 80 percent of all pregnancies, whereas in Kurdish Jews they constitute only 64 percent of the total fertility. The average birth weight of infants of all parities surviving for at least one month was 3023 ± 69 gm. for males ($N = 24$) and 2840 ± 71 gm. for females ($N = 26$). These weights are even lower than those for the first parities alone in Kurdish infants (see p. 348).

Among the interesting features noted during the medical examination was the slow reaction to ocular atropine administration. The time required for pupil dilatation was at least twice as long as in children of the Kurdish community.*

* This work was supported by a grant from the Ford Foundation.

GENE FLOW BETWEEN SETTLEMENTS IN COCHIN



ARROWS POINT TO GROOMS' DOMICILES

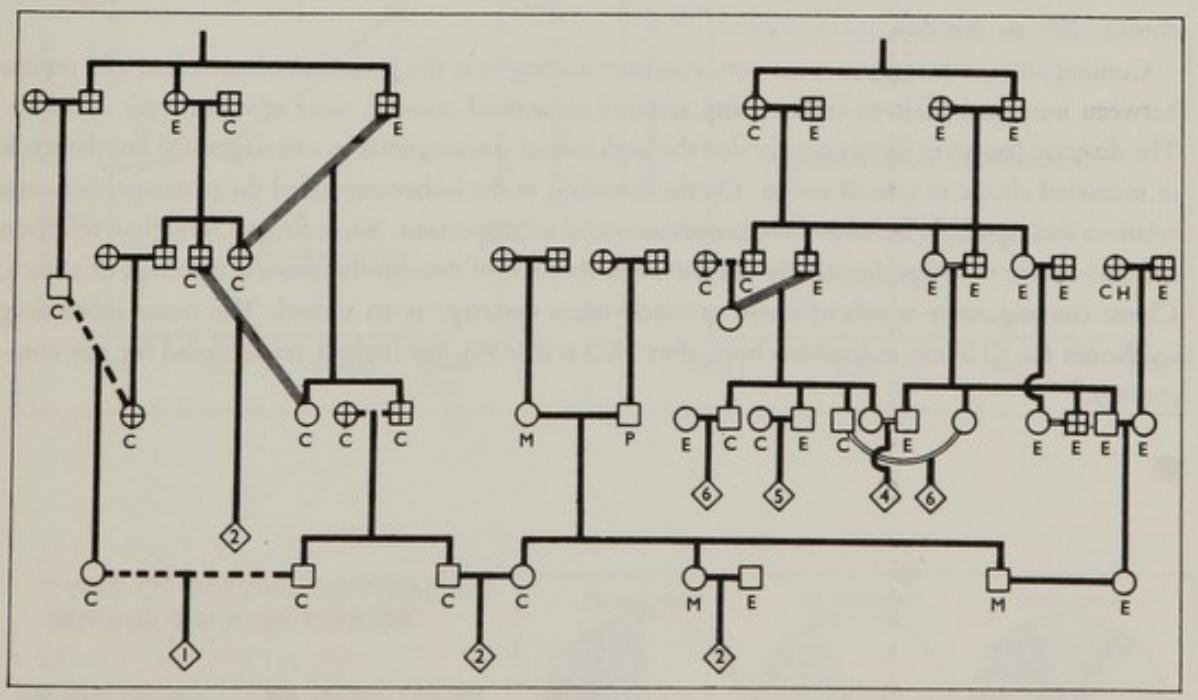
NUMBERS BESIDE ARROWS: EXOGAMOUS WIVES
NUMBERS IN CIRCLES: ENDOGAMOUS WIVES

0 5 Km.

ENDOGAMOUS AND EXOGAMOUS WIVES: 60 IMMIGRANT COUPLES

ENDOGAMOUS AND EXOGAMOUS WIVES: 87 COUPLES OF THE GRANDPARENTAL GENERATION

CLAN OF COCHIN JEWS



BIRTH PLACES

C: COCHIN
E: ERNACULAM
CH: CHENNAMANGALAM
P: PARUR
M: MALA

◇2 TWO INFANTS BORN ALIVE
⊕⊞ DECEASED

UNCLE-NIECE MARRIAGE
COUSIN MARRIAGE
MARRIAGE BETWEEN MORE DISTANT RELATIVES

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Hebrew University
Jerusalem, Israel

A GROUP OF three hundred individuals who call themselves Samaritans trace their ancestry over a period of more than 2000 years from the Biblical Samaritans. This group is now divided into two parts living under different political allegiances—Jordan and Israel—but in the same general geographic area that they have never left during that period.

The Samaritan tradition is an offshoot of the Jewish religion, with which a split occurred in 500 B.C. over the question of the location of the temple as well as other matters. The history of the group since then has been a long succession of misfortunes suffered from oppression and massacres. From a nation consisting initially of several hundred thousands the Samaritans gradually became a small sect, reaching their minimum number of 150 at the end of the nineteenth century. Despite this fact, from a few centuries B.C. to the present date, they have remained strictly endogamous.

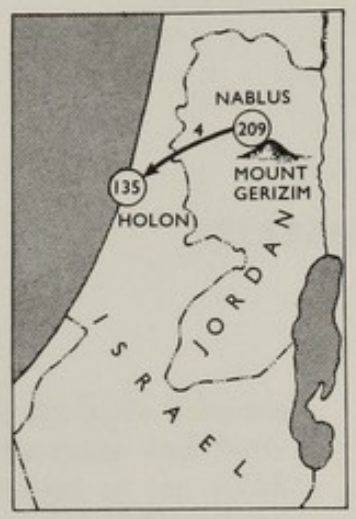
The demographic data presented here cover the period from 1900 to 1960. They were assembled from a Census Report (1931)[12] and from the notes of previous investigators[99] but in particular from the information obtained in a prolonged correspondence with a member the of Samaritan community, whose invaluable cooperation is here gratefully acknowledged.[210]

By 1900 the Samaritan community had dwindled to 150 individuals. Since then the population has more than doubled. In 1960 it comprised 343 persons, of whom 209 resided in Nablus in Jordan territory (see map) and 134 were settled in Holon (Israel).

The over-all sex ratio of this group has undergone large fluctuations in recent decades. In 1900 it was extremely high (176), but by 1930 had dropped to 90. In 1960 it was 120, again somewhat high. The graph (left center) shows that the average age of women at marriage has risen steadily during the past 60 years. This may be ascribed in part to the expansion of the isolate and in part to the near-normalization of the sex ratio. In former years Samaritan men solved the problem of scarcity of women by "borrowing" their spouses from the next generation. In those days the mean age discrepancy between mates was very large and although it has decreased by now (see right center) it is very considerable to this day.

Consanguineous marriages were very common throughout the period of observation, and unions between unrelated partners (relationship remoter than third cousins) were always in the minority. The diagram (bottom) shows clearly that the high rate of consanguineous marriages was not the result of restricted choice in a small isolate. On the contrary, as the isolate expanded the marriages between relatives and especially between first cousins increased in proportion. According to Samaritan tradition the first-cousin marriage (especially that between children of two brothers) is the marriage of choice. Closer consanguinity is unlawful and no uncle-niece marriage is on record. The mean inbreeding coefficient for all living individuals born after 1933 is 0.04345, the highest yet recorded for any community.*

* This report is based on a section of an M.S. thesis in the Department of Anthropology, University of Chicago, Chicago, Ill. The author wishes to express her sincere thanks to Dr. S. M. Garn of the Fels Research Institute, Yellow Springs, Ohio, for his interest and encouragement. Thanks are also due to Dr. D. F. Roberts, of the Department of Anatomy, Oxford, England, for his helpful suggestions and criticism.



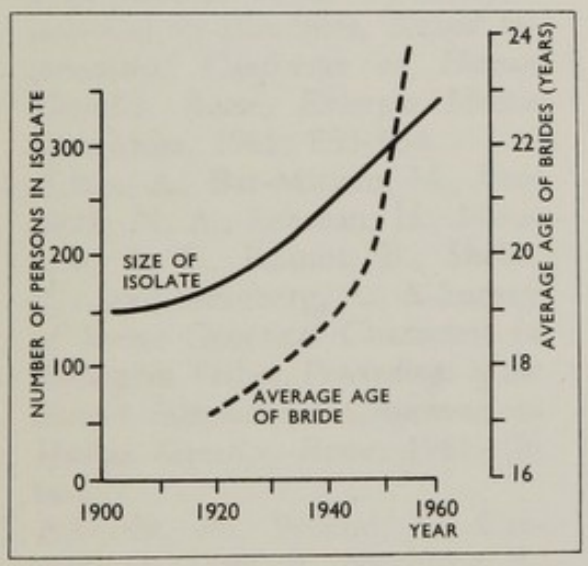
THE SAMARITAN SETTLEMENTS

135 MEMBERS SETTLED IN ISRAEL
209 MEMBERS SETTLED IN JORDAN
MEET ANNUALLY ON MOUNT GERIZIM
FOR PASSOVER CELEBRATIONS

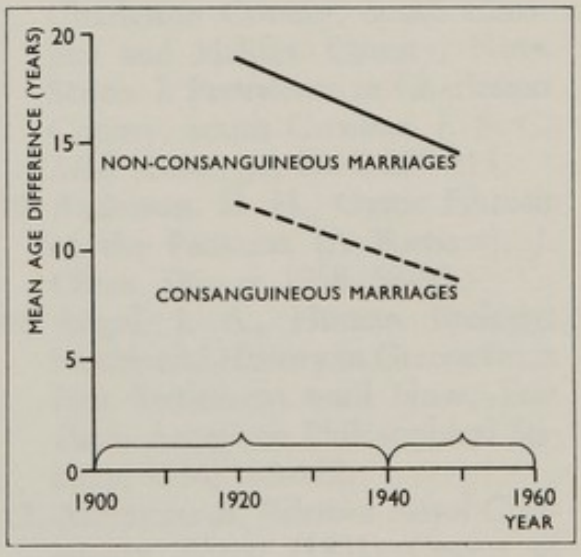
4: FOUR BRIDES MIGRATED
TO ISRAEL (1951-1960)

TIME TRENDS

SIZE OF ISOLATE AND AGE OF BRIDES

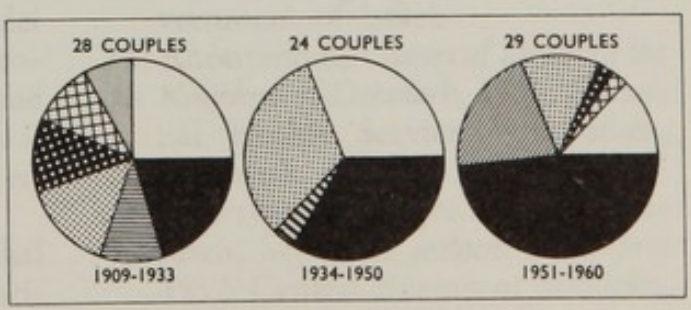


AGE DIFFERENCE BETWEEN MATES



TYPES OF UNIONS CONTRACTED DURING VARIOUS PERIODS

- FIRST COUSINS
- FIRST COUSINS ONCE REMOVED
- FIRST COUSINS TWICE REMOVED
- SECOND COUSINS
- SECOND COUSINS ONCE REMOVED
- THIRD COUSINS
- UNRELATED
- UNKNOWN



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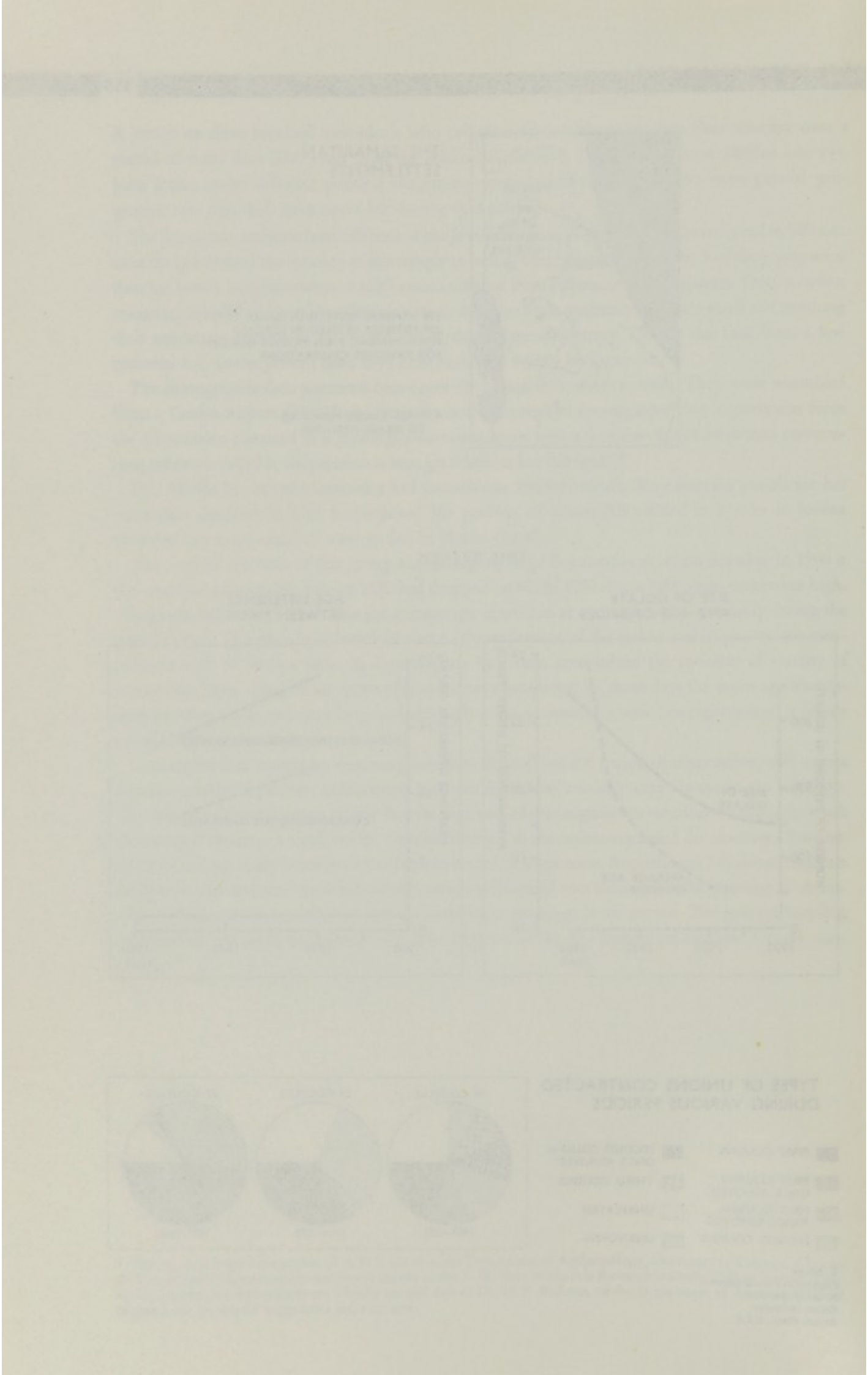

REFERENCES

1. Acheson, E. D., Multiple Sclerosis Frequency in Australia and New Zealand, *Proceedings of the VIIth International Congress of Neurology,* 1962. (In press.)
2. Adam, A., Linkage between Deficiency of Glucose-6-Phosphate Dehydrogenase and Colour-Blindness, *Nature, 189,* 1961, 686.
3. Adam, A., Linkage between Enzyme Deficiency of Erythrocytes and Colour-Blindness, *Second International Conference on Human Genetics, Rome, Excerpta Medica Foundation,* 1961, E53-E54.
4. Adam, A., Bat-Miriam, M., Barnicot, N. A., Lehman, H., Mourant, A. E., Ramot, B., Sheba, Ch., and Szeinberg, A., A Survey of Some Genetical Characters in Ethiopian Tribes, *Proceedings of the Second International Conference on Human Genetics, Rome,* 1961. (In press.)
5. Adinolfi, M., Bernini, L., Carcassi, U., Latte, B., Motulsky, A. G., and Siniscalco, M., Indagini genetiche sulla predisposizione al favismo.—I. Il problema ed i metodi. Fluttuazioni stagionali dei livelli di glucose-6-fosfato-deidrogenasi in Sardegna. Interazione con la talassemia al livello fisiologico, *R. Accad. Naz. Lincei.,* Ser. VIII, *28,* fasc. 5, 1960, 1-11.
6. Aharoni, Y., The Caves of Nahal Hever, *Atiqot, J. Isr. Dept. Antiquit., 3,* 1961, 148-162.
7. Aharoni, Y., The Expedition to the Judean Desert 1960, Expedition B, *Israel Explor. J.,* 11, 1961, 11-24.
8. Allison, R. S., and Millar, J. H. D., Prevalence and Familial Incidence of Disseminated Sclerosis, *Ulster Med. J., 23* (suppl. 2), 1954, 1-92.
9. Alter, M., Allison, R. S., Talbert, O. R., and Kurland, L. T., The Geographic Distribution of Multiple Sclerosis. A Comparison Study in Charleston County, South Carolina and Halifax County, Nova Scotia. I. Prevalence in Charleston County, South Carolina, *J. S. C. Med. Assoc., 56,* 1960, 209-213.
10. Anderson, D. H., Cystic Fibrosis of the Pancreas (A Review), *J. Chron. Dis., 7,* 1958, 58-90.
11. Angel, J. A., Human Biology, Health and History in Greece from First Settlement until Now, *Year Book,* American Philosophical Society, 1954, 168-172.
12. Anonymous, *Palestine Royal Commission Report* (1931), Census of Palestine, London.
13. Anonymous, Unpublished data, Statistical Bureau (1948-1958), Government of Israel.
14. Anonymous, *Causes of Death in the Kingdom of Denmark,* 1950, National Health Service Publication, Denmark, 1951.
15. Anonymous, *Sterfte naar doodsoorsaken, leeftijd en geslacht in het jaar* 1952, Central Bureau of Statistics, Amsterdam, 1953.
16. Anonymous, *The Registrar Gene-*

ral's Review of England and Wales for the Year 1952, London, 1953.
17. Anonymous, *Annual Epidemiological and Vital Statistics for the Year 1952,* World Health Organization, 1955.
18. Anonymous, *Statistical Abstract of Israel,* No. 10, 1958-59, Government Printer, Jerusalem.
19. Anonymous, Live Births and Still Births in Hospitals and Outside of Hospitals (Hebrew), *Stat. Month. Israel, 10,* 1959, 315.
20. Archer, H. H., Dormer, A. E., Scowen, E. F., and Watts, R. W. E., Observations on the Possible Genetic Basis of Primary Hyperoxaluria, *Ann. Hum. Gen., London, 22,* 1958, 373-379.
21. Armstrong, A. R., and Peart, H. E., A Comparison between the Behavior of Eskimos and Non-Eskimos to the Administration of Isoniazid, *Am. Rev. Resp. Dis., 81,* 1960, 588-594.
22. Aronson, S. M., Aronson, E., and Bruno, W. V., A Genetic Profile of Infantile Amaurotic Family Idiocy, *A. M. A. J. Dis. Child., 98,* 1959, 50-65.
23. Aronson, S. M., and Volk, B. W., (Eds.), *Cerebral Sphingolipidoses. A Symposium on Tay-Sachs' Disease and Allied Disorders,* Academic Press, Inc. N.Y., 1962.
24. Atsmon, A., Frank, M., Lazebnik, J., Kochwa, S., and De Vries, A., Uric Acid Stones: A Study of 58 Patients, *J. Urol., 84,* 1960, 167-176.
25. Avigad, N., The Expedition to the Judean Desert, Expedition A, *Israel Explor. J., 11,* 1961, 6-10.
26. Bar-Adon, P., The Expedition to the Judean Desert 1960, Expedition C, *Israel Explor. J., 11,* 1961, 25-35.
27. Barnes, H. D., and Bloomberg, B. M., Paper Chromatography of Urinary Sugar in Essential Pentosuria, *S. Afr. J. M. Sc., 18,* 1953, 93-98.
28. Bell, J., A Determination of the Consanguinity Rate in the General Hospital Population of England and Wales, *Ann. Eug., 10,* 1940, 370-391.
29. Bell, J. C., and Riemensnider, D. K., Use of Serum Microbiologic Assay Technique for Estimating Patterns of Isoniazid Metabolism, *Am. Rev. Tuberc., 75,* 1957, 995-998.
30. Bender, M. A., and Gooch, P. C., Persistent Chromosome Aberrations in Irradiated Human Subjects, *Radiation Res., 16,* 1962, 44-53.
31. Benhamou, E., Albou, A., and Sayag, P., La maladie périodique, *Algérie Méd., 59,* 1955, 809-818.
32. Ben-Jacob, A., *Kurdistan Jewish Communities* (Hebrew), Ben-Zvi Institute, Hebrew University, Jerusalem, 1961.
33. Berman-Yeshurun, T., Morbidity in the Old Populations and in the Newcomers since the Establishment of the State of Israel, *Dapim Refuiim, 15,* 1956, 54-59.
34. Bernini, L., Carcassi, U., Latte, B., Motulsky, A. G., Romei, L., and Siniscalco, M., Indagini genetiche sulla predisposizione al favismo. III. Distribuzione delle frequenze geniche per il locus Gd in Sardegna. Interazione con la malaria e la talassemia al livello popolazionistico, *R. Accad. Naz. Lincei,* Ser. VIII, *29,* fasc. 1-2, 1960, 1-11.
35. Berry, K. H., Cystinuria in Mentally Retarded Siblings with Atypical Osteogenesis Imperfecta, *A. M. A. J. Dis. Child., 97,* 1959, 196-197.
36. Beutler, E., The Glutathione Instability of Drug-Sensitive Red Cells. A New Method for the In Vitro Detection of Drug Sensitivity, *J. Lab. Clin. Med., 49,* 1957, 84-95.
37. Blondheim, S. H., and Kallner, G., Incidence of Diseases among the

Communities of Israel, *Harefuah, 51,* 1956, 81-84.
38. Böök, J. A., The Incidence of Congenital Diseases and Defects in a South Swedish Population, *Acta Genet. Stat. Med., 2,* 1951, 289-311.
39. Boyce, W. H., Garvey, F. K., and Strawcutter, H. E., Incidence of Urinary Calculi among Patients in General Hospitals, 1948-1952, *J. A. M. A., 161,* 1956, 1437-1442.
40. Boyd, E., Buchanan, W. W., and Lennox, B., Damage to Chromosomes by Therapeutic Doses of Radioiodine, *Lancet, i,* 1961, 977-978.
41. Brand-Auraban, A., The Epidemiology of Rheumatic Fever in Israel, *Harefuah, 57,* 1959, 53-58.
42. Brittingham, T. E., Immunologic Studies on Leukocytes, *Vox. Sang., 2,* 1957, 242-248.
43. Brunner, D., Altmann, S., Loebl, K., Nelken, L., and Reider, J., Occlusive Vascular Disease in Diabetes. I. A Study of Clinical Findings in Diabetic Yemenite Jews, 1962. (In press.)
44. Brunner, D., Altmann, S., Loebl, K., Nelken, L., and Reider, J., Occlusive Vascular Disease in Diabetes. II. Relationship of Lipid-Pattern to Vascular Complications in Diabetic Yemenite Jews, 1962. (In press.)
45. Brunner, D., Altmann, S., Loebl, K., and Schwartz, S., Lipoprotein Patterns of Middle Aged Coronary Patients with and without Increased Total Serum Cholesterol. (In press.)
46. Brunner, D., and Loebl, K., Serum Cholesterol, Electrophoretic Pattern, Diet and Coronary Artery Disease: A Study in Coronary Patients and in Healthy Men of Different Origin and Occupations in Israel, *Ann. Int. Med., 49,* 1958, 732-750.
47. Brunner, D., and Manelis, G., Myocardial Infarction among Members of Communal Settlements in Israel, *Lancet, ii,* 1960, 1049-1050.
48. Brunner, D., Manelis, G., and Loebl, K., Influence of Age and Race on Lipid Levels in Israel, *Lancet, i,* 1959, 1071-1073.
49. Brzezinski, A., Gurevitch, J., Hermoni, D., and Mundel, G., Blood Groups in Jews from the Yemen, *Ann. Eug. Lond., 16,* 1952, 335-337.
50. Byfogle, J. W., and Bradley, R. F., The Vascular Complications of Diabetes Mellitus, A Clinical Study, *Diabetes, 6,* 1957, 159-167.
51. Carter, O. C., The Inheritance of Congenital Pyloric Stenosis, *Brit. Med. Bull., 17,* 1961, 251-253.
52. Casper, J., Incidence of Uterine Cancer among Different Ethnic Groups, *Schweiz. Ztschr. Allgem. Pathol. Bakt., 18,* 1955, 764-774.
53. Centerwall, W. R., Phenylketonuria—A General Review, *J. Am. Diet. Assoc., 36,* 1960, 201-205.
54. Chanarin, J., Dacie, J. V., and Mollin, D. L., Folic Acid Deficiency in Haemolytic Anaemia, *Brit. J. Haem., 5,* 1959, 245-256.
55. Chanarin, J., MacGibbon, M. B., O'Sullivan, W. J., and Mollin, D. L., Folic Acid Deficiency in Pregnancy. The Pathogenesis of Megaloblastic Anaemia of Pregnancy, *Lancet, ii,* 1959, 634-639.
56. Chanarin, J., Mollin, D. L., and Anderson, B. B., The Clearance from the Plasma of Folic Acid Injected Intravenously in Normal Subjects and Patients with Megaloblastic Anaemia, *Brit. J. Haem., 4,* 1958, 435-446.
57. Childs, B., Zinkham, W., Browne, E. A., Kimbro, E. L., and Torbert, J. V., A Genetic Study of a Defect in Glutathione Metabolism of the Erythrocyte, *Bull. Johns Hopkins Hosp., 102,* 1958, 21-37.
58. Chowers, I., Czaczkes, J. W.,

Ehrenfeld, E. N., and Landau, S., Familial Amino-Aciduria in Osteogenesis Imperfecta, 1962. (In press.)
59. Cohen, A. M., Prevalence of Diabetes among Different Ethnic Jewish Groups in Israel, *Metabolism, 10,* 1961, 50-58.
60. Cohen, A. M., Neumann, E., and Michaelson, I. C., Involutionary Sclerosis and Diastolic Hypertension, *Lancet, ii,* 1960, 1050-1051.
61. Cohen, B. E., Szeinberg, A., and Bodonyi, E., Phenylketonuria among Jews, *Lancet, i,* 1961, 344-345.
62. Cohen, B. E., Szeinberg, A., Boichis, H., Pollak, E., Bodonyi, E., Hirschorn, N., and Bar-Or, R., Phenylketonuria among Jews, *Bull. Res. Council Israel, 10,* 1961, 1.
63. Cohen, P., and Kozin, P. J., Phenylpyruvic Oligophrenia in a Jewish Child, *J. Ped., 34,* 1949, 76-79.
64. Cohen, T., Goldschmidt, E., Adam, A., Matoth, Y., Theodor, E., and Szabo, M. A., The Frequency of Rheumatic Heart Disease, Glutathione Instability and Thalassemia in Children of Kurdish Jews, *Harefuah, 57,* 1959, 233-236.
65. Coon, C. S., *The Races of Europe,* Macmillan Co., New York, 1939.
66. Cowie, V., and Penrose, L. S., Dilution of Hair Colour in Phenylketonurics, *Ann. Eug., London, 15,* 1951, 297-301.
67. Cummins, H., and Midlo, C., *Finger Prints, Palms and Soles: An Introduction to Dermatoglyphics,* Blakiston, Philadelphia, 1943.
68. Da Cunha, A. X., and Abreu, M. D. A., Impressoes digitais de Portugueses, *Contr. Antrop. Portug., 5,* 1954, 315-347.
69. Danon, D., Sheba, Ch., and Ramot, B., The Morphology of Glucose-6-Phosphate Dehydrogenase Deficient Erythrocytes: Electron-Microscopic Studies, *Blood, 17,* 1961, 229-234.
70. Dausset, J., Iso-Leuco-Anticorps, *Acta haemat., 20,* 1958, 156-166.
71. Dausset, J., and Brecy, H., Identical Nature of the Leukocyte Antigens Detectable in Monozygotic Twins by Means of Immune Iso-Leuco-Agglutinins, *Nature, 180,* 1957, 1430.
72. Davies, M., and Lazarov, E., Heredity, Infection and Chemoprophylaxis in Rheumatic Carditis: An Epidemiological Study of a Communal Settlement, *J. Hyg. Camb., 58,* 1960, 263-276.
73. Deniker, J., *Les Races et Peuples de la Terre,* Masson, Paris, 1926.
74. De Vries, A., Kochwa, S., Lazebnik, J., Frank, M., and Djaldetti, M., Glycinuria, a Hereditary Disorder Associated with Nephrolithiasis, *Am. J. Med., 23,* 1957, 408-415.
75. Di Sant'Agnese, P. A., Cystic Fibrosis of the Pancreas: Clinical Staff Conference at the National Institutes of Health, *Ann. Int. Med., 54,* 1961, 482-502.
76. Dreyfuss, F., The Incidence of Myocardial Infarctions in Various Communities in Israel, *Am. Heart J., 45,* 1953, 749-755.
77. Dreyfuss, F., Cooley's Trait in Oriental Jews, *Bull. Res. Council Israel, 4,* 1955, 402.
78. Dreyfuss, F., La Thalassémie Mineure (Cooley) dans trois Familles Juives Orientales, *J. Génét. Hum., 4,* 1955, 143-151.
79. Dreyfuss, F., and Hamosh, P., A Coronary Disease Study among Cochin Jews in Israel, *Am. J. Med. Sc., 240,* 1960, 769-775.
80. Dreyfuss, F., Toor, M., Agmon, J., and Zlotnik, A., Observations on Myocardial Infarctions in Israel, *Cardiologia, 6,* 1957, 387-398.
81. Dunn, L. C., and Dunn, S. P., The Jewish Community of Rome, *Scientific American, 196,* 1957, 119-128.
82. Engelfriet, C. P., and Loghem, J.

J., Studies on Leucocyte Iso- and Auto-Antibodies, *Brit. J. Haem., 7,* 1961, 223-238.
83. Epstein, F. M., and Boas, E. P., Prevalence of Manifest Atherosclerosis among Italian and Jewish Garment Workers, *J. Geront., 10,* 1955, 331-337.
84. Falk, W., and Gellei, B., The Familial Occurrence of Letterer-Siwe Disease, *Acta paediat., 6,* 1957, 471-480.
85. Field, H., *Ancient and Modern Man in Southwestern Asia,* University of Miami Press, Florida, 1956.
86. Fischel, W. J., *The Jews in India* (Hebrew), Ben-Zvi Institute, Hebrew University, Jerusalem, 1960.
87. Franceschetti, A., and Klein, D., Les Affections génétiques en Ophtalmologie, *Encyclopédie Med.-Chirurg., 21,* Laffont and Duriex, Paris, 1955.
88. Franceschetti, A., Klein, D., and Babel, J., Les manifestations oculaires des troubles primitifs du metabolisme des lipides. Étude clinique, génétique et anatomopathologique, *Arq. Neuro-psiquiatria, 13,* 1955, 69-160.
89. Franco, S., Studies in Gaucher's Disease, *Harefuah, 25,* 1943, 143-145.
90. François, J., Verriest, G., Mortier, V., and Vanderdonck, R., De la fréquence des dyschromatopsies congénitales chez l'homme, *Ann. Oculist. Paris, 189,* 1957, 5-16.
91. Frank, M., Atsmon, A., and De Vries, A., Inherited Uric Acid Lithiasis, *Am. J. Med.,* 1962. (In press.)
92. Frank, M., Atsmon, A., Sugan, P., and De Vries, A., Epidemiological Investigation of Urolithiasis in the Hot and Southern Region of Israel, *Urologia Internationalis,* 1962. (In press.)
93. Frank, M., De Vries, A., Atsmon, A., Lazebnik, J., and Kochwa, S., Epidemiological Investigation of Urolithiasis in Israel, *J. Urol., 81,* 1959, 497-505.
94. Fried, K., Gaucher's Disease among the Jews of Israel, *Bull. Res. Council Israel, 7 B,* 1958, 213.
95. Frischknecht, W., Bianchi, L., and Pilleri, G., Arthrogryposis Multiplex Congenita, *Helv. Paed. Acta, 15,* 1960, 259-279.
96. Frota-Pessoa, O., The Estimation of the Size of Isolates Based on Census Data, *Am. J. Human Gen., 9,* 1957, 9-16.
97. Galatius-Jensen, F., *The Haptoglobins, A Genetical Study,* Dans Videnskabs Forlag, Copenhagen, 1960.
98. Garrod, A. E., The Incidence of Alkaptonuria: A Study in Chemical Individuality, *Lancet, ii,* 1902, 1616-1620.
99. Genna, G., Anthropologia Samaritani, *Spedizioni Scientifiche del Comitato Italiano per lo Studio dei problemi della popolazione, Vol. I, Ser. V,* 1938, Rome.
100. Gilboa-Garber, N., and Nelken, D., Specific Antigens of Human Leucocytes and Thrombocytes, *Nature, 192,* 1961, 466-467.
101. Goldschmidt, E., Bayani-Sioson, P., Sutton, H. E., Fried, K., Sandor, A., and Bloch, N., Haptoglobin Frequencies in Jewish Communities, *Ann. Hum. Gen.,* London, *26,* 1962, 39-46.
102. Goldschmidt, E., Cohen, T., Bloch, N., Flum, Y., and Kadar, M., A Family Study of School Attainments (Hebrew), *Megamot, 11,* 1961, 345-356.
103. Goldschmidt, E., Ronen, A., and Ronen, I., Changing Marriage Systems in the Jewish Communities of Israel, *Ann. Hum. Gen., 24,* 1960, 191-204.
104. Gore, I., and Tejada, C., The Quantitative Appraisal of Athero-

sclerosis, *Am. J. Path., 33,* 1957, 875-885.
105. Groen, J., The Hereditary Mechanism of Gaucher's Disease, *Blood, 3,* 1948, 1238-1249.
106. Groen, J., and Garrer, A. H., Adult Gaucher's Disease with Special Reference to the Variations in Its Clinical Course and the Value of Sternal Puncture as an Aid to Its Diagnosis, *Blood, 3,* 1948, 1221-1237.
107. Grossowicz, N., Aronovitch, J., Rachmilewitz, M., Izak, G., Sadowsky, A., and Bercovici, B., Folic and Folinic Acid in Maternal and Foetal Blood, *Brit. J. Haem., 6,* 1960, 296-302.
108. Gurevitch, J., Hasson, E., Margolis, E., and Polishuk, Z., Blood Groups in Jews from Cochin, India, *Ann. Human Gen.,* London, *19,* 1955, 254-256.
109. Gurevitch, J., Hasson, E., Margolis, E., and Poliakoff, C., Blood Groups in Jews from Tripolitania, *Ann. Eug.,* London, *19,* 1955, 260-261.
110. Gurevitch, J., Hasson, E., and Margolis, E., Blood Groups in Persian Jews, *Ann. Eug.,* London, *21,* 1956, 135-138.
111. Gurevitch, J., Hermoni, D., and Polishuk, Z., Rh Blood Types in Jerusalem Jews, *Ann. Eug.,* London, *16,* 1951, 129-130.
112. Gurevitch, J., Hermoni, D., and Margolis, E., Blood Groups in Kurdistani Jews, *Ann. Eug.,* London, *18,* 1953, 94-95.
113. Gurevitch, J., and Margolis, E., Blood Groups in Jews from Iraq, *Ann. Human Gen.,* London, *19,* 1955, 257-259.
114. Guttman, L., A Generalized Simplex for Factor Analysis, *Psychometrika, 20,* 1955, 173-192
115. Hagberg, M., Personal Communication, Swedish Institute and Swedish Committee on International Health Relations.
116. Hakim, S. A. E., Mijovic, V., and Walker, J., Distribution of Certain Poppy-Fumaria Alkaloids and a Possible Link with the Incidence of Glaucoma, *Nature, 189,* 1961, 198-201.
117. Halevi, H. S., and Landau, J., Hospitalized Senile Cataract in Different Jewish Communities in Israel, *Brit. J. Ophthal., 46,* 1962, 285-290.
118. Hanhart, E., Über 27 Sippen mit Infantiler Amaurotischer Idiotie (Tay-Sachs), *Acta Genet. Med. et Gemell., 3,* 1954, 331-364.
119. Harris, H., *Human Biochemical Genetics,* Cambridge University Press, 1959.
120. Harris, H. A., and Kalmus, H., The Measurement of Taste Sensitivity to Phenylthiourea (P.T.C.), *Ann. Eug.,* London, *15,* 1950, 24-31.
121. Harris, H. W., Knight, R. A., and Selin, M. J., Comparison of Isoniazid Concentrations in the Blood of People of Japanese and European Descent, *Am. Rev. Tuberc., 78,* 1958, 944-948.
122. Heller, H., Sohar, E., and Sherf, L., Familial Mediterranean Fever, *Arch. Int. Med., 102,* 1958, 50-71.
123. Heller, H., Sohar, E., Gafni, J., and Heller, J., Amyloidosis in Familial Mediterranean Fever, *Arch. Int. Med., 107,* 539-550.
124. Hendel, H., and Ben-Assa, B. J,. Report about a Beduin Family Affected by Alkaptonuria, *Ann. Paediat.* (Basel), *195,* 1960, 77-87.
125. Hiatt, H. H., Carbohydrate Metabolism in Pentosuria, *Ann. Int. Med., 53,* 1960, 372-379.
126. Hillman, J. W., and Johnson, J. T. H., Arthrogryposis Simplex Congenita in Twins, *J. Bone Joint Surg., 34 A,* 1952, 211-214.
127. Holt, S., A Quantitative Survey of the Finger Prints of a Small Sample of the British Population, *Ann. Eug., 14,* 1949, 329-338.

128. Hossi, E., and Calflisch, A., Le syndrome du pterygium, *Helv. Paed. Acta, 6,* 1951, 119-148.
129. Hungerford, D. A., Chromosome Studies in Human Leukemia. I. Acute Leukemia in Children, *J. Nat. Cancer Inst., 27,* 1961, 983-1011.
130. Hyllested, K., *Disseminated Sclerosis in Denmark, Prevalence and Geographic Distribution,* Jorgensen, Copenhagen, 1956.
131. Izak, G., Rachmilewitz, M., Stein, Y., Bercovici, B., Sadovsky, A., Aronovitch, J., and Grossowicz, N., Vitamin B_{12} and Iron Deficiency Anemia in Pregnancy and Puerperium, *Arch. Int. Med., 99,* 1957, 346-355.
132. Jervis, G. A., Genetics of Phenylpyruvic Oligophrenia, *J. Ment. Sc., 85,* 1939, 719-762.
133. Jervis, G. A., Detection of Heterozygotes for Phenylketonuria, *Clin. Chim. Acta, 5,* 1960, 471-476.
134. Kagan, H., Problems of Diagnosis of Rheumatic Fever, *Harefuah, 50,* 1956, 133-134.
135. Kallner, G., *Cancer Mortality in Israel 1950-1957,* Special Series of Publications, Central Bureau of Statistics, Jerusalem, No. 107, 1961.
136. Kalmus, H., Amir, A., Levine, O., Barak, E., and Goldschmidt, E., The Frequency of Inherited Defects of Colour Vision in Some Israeli Populations, *Ann. Human Gen.,* London, *25,* 1961, 51-55.
137. Kappers, C. U. A., and Parr, L. W., *An Introduction to the Anthropology of the Near-East, in Ancient and Recent Times,* Noord-Hollandsche Uitgeversmaatschappij, Amsterdam, 1934.
138. Kass, I., Russel, W. F., Heaton, A., Miyamoto, T., Middlebrook, G., and Dressler, S. H., Changing Concepts in the Treatment of Pulmonary Tuberculosis, *Ann. Int. Med., 47,* 1957, 744-761.
139. Katzuni, E., and Sandbank, U., Oxalosis, *Arch. Dis. Child., 34,* 1959, 60-62.
140. Keys, A., Michelson, O., Meller, E. V. O., Hages, E. R., and Todd, R. L., Concentration of Cholesterol in Blood Serum of Normal Men and its Relation to Age, *J. Clin. Invest., 29,* 1950, 1347-1353.
141. Klein, D., and Kténidès, M. A., Au sujet de l'hérédité de l'idiotie amaurotique infantile (Tay-Sachs), *J. Génét. Hum., 3,* 1954, 184-202.
142. Klibansky, Ch., Djaldetti, M., Joshua, H., and De Vries, A., Hemoglobin H-Thalassemia Disease in a Sephardic Jewish Family from Turkey, *Isr. Med. J., 19,* 1960, 199-202.
143. Knight, R. A., Selin, M. J., and Harris, H. W., Genetic Factors Influencing Isoniazid Blood Levels in Humans, *Trans. Conf. Chemother. Tuberc., 18,* 1959, 52-59.
144. Koch, B., Hereditary Adult Mucoviscidosis and its Relationship to Peptic Ulcer, *German Med. Monthly, 5,* 1960, 40-46.
145. Kozinn, P. J., Wiener, H., and Cohen, P., Infantile Amaurotic Family Idiocy, *J. Ped., 51,* 1957, 58-64.
146. Kurland, L. T., and Westlund, K. B., Epidemiologic Factors in the Etiology and Prognosis of Multiple Sclerosis, *Ann. N.Y. Acad. Sc., 58,* 1954, 682-701.
147. Lalezari, P., and Spaet, T. H., Studies on the Genetics of Leukocyte Antigens, *Blood, 14,* 1959, 748-758.
148. Landau, J., and Halevi, H. S., Incidence of Glaucoma in Various Ethnic Groups in the Population of Israel, *Brit. J. Ophthal., 44,* 1960, 751-754.
149. Laron, Z., Incidence of Hypertrophic Pyloric Stenosis in the various Jewish Communities in Israel, *Acta paediat., 44,* 1955, 40-44.
150. Laron, Z., and Falk, R., Comments on Ethnic Differences in the Inci-

dence of Infantile Pyloric Stenosis, *Bull. Res. Council Israel, 7 B,* 1958, 218-219.
151. Laron, Z., and Horne, L. M., The Incidence of Infantile Pyloric Stenosis, *A.M.A.J. Dis. Child., 94,* 1957, 151-154.
152. Laron, Z., Yonis, Z., and Bornstein, B., Phenylketonuria in Jews *Pediatrics, 26,* 1960, 885.
153. Larson, H. W., Blatherwick, N. R., Bradshaw, P. J., Ewing, M. E., and Sawyer, S. D., The Metabolism of d-Xylulose, *J. Biol. Chem., 117,* 1937, 719-725.
154. Lasker, M., Enklewitz, M., and Lasker, G. W., Inheritance of l-Xyloketosuria (Essential Pentosuria), *Human Biol., 8,* 1936, 243-255.
155. Lawson, D., The Incidence of Pyloric Stenosis in Dundee, *Arch. Dis. Child., 26,* 1951, 616-617.
156. Lévêque, J., Les groupes sanguins des populations Marocaines, *Bull. Inst. Hyg. Maroc., 15,* 1955, 237-321.
157. Lundman, B., Blutgruppen und Stammeskunde der Juden, *Orientalia Suecana, 6,* 1957, 107-114.
158. Lyon, M. F., Sex Chromatin and Gene Action in the Mammalian X-Chromosome, *Am. J. Human Gen., 14,* 1962, 135-148.
159. Mamouh, H., and Cattan, R., La maladie périodique, *Semaine Hôp. Paris, 28,* 1952, 1062-1070.
160. Margolis, E., Gurevitch, J., and Hasson, E., Blood Groups in Jews from Morocco and Tunisia, *Ann. Human Gen.,* London, *22,* 1957, 65-68.
161. Martin, R., and Saller, K., *Lehrbuch der Anthropologie, II,* G. Fischer, Stuttgart, 1959.
162. Matoth, Y., Thalassemia in a Damascus Jewish Family, Personal Communication, 1962.
163. Matoth, Y., and Pinhas, J., Thalassemia in Jews from Kurdistan, *Bull. Res. Council Israel, 7 B,* 1958, 215.
164. Matoth, Y., Shamir, Z., and Freundlich, E., Thalassemia in Jews from Kurdistan, *Blood, 10,* 1955, 176-189.
165. McKeown, T., MacMahon, B., and Record, R. G., The Incidence of Congenital Pyloric Stenosis Related to Birth Rank and Maternal Age, *Ann. Eug.,* London, *16,* 1951, 249-259.
166. McKeown, T., MacMahon, B., and Record, R. G., Evidence of Post-natal Environmental Influence in the Aetiology of Infantile Pyloric Stenosis, *Arch. Dis. Child., 27,* 1952, 386-390.
167. McKeown, T., and Record, R. G., Malformations in a Population Observed for Five Years after Birth, in *Ciba Foundation Symposium on Congenital Malformations,* Churchill, London, 1960, pp. 2-21.
168. McLaurin, A. W., Beisel, W. R., McCormick, G. J., Scalettar, R., and Herman, R. H., Primary Hyperoxaluria, *Ann. Int. Med., 55,* 1961, 70-80.
169. Meital, V., Izak, G., and Rachmilewitz, M., L'effet de la grossesse sur la thalassémie, *Nouv. Rev. Franc. Hémat., 1,* 1961, 389-409.
170. Merin, S., *Congenital Malformations,* Unpublished M.D. Thesis, Hebrew University-Hadassah Medical School, 1960.
171. Messerlin, A., *Groupes sanguins et facteur rhésus au Maroc,* Unpublished Thesis, 1950, 78 pp.
172. Milch, R. A., Direct Inheritance of Alcaptonuria, *Metabolism, 4,* 1955, 513-518.
173. Milch, R. A., Studies of Alcaptonuria: Inheritance of 47 Cases in Eight Highly Inter-Related Dominican Kindreds, *Am. J. Human Gen., 12,* 1960, 76-85.
174. Morton, N. E., Non-Randomness in Consanguineous Marriages, *Ann. Human Gen.,* London, *20,* 1955, 116-124.

175. Morton, N. E., Empirical Risks in Consanguineous Marriages: Birth Weight, Gestation Time and Measurements of Infants, *Am. J. Human Gen., 10,* 1958, 344-349.
176. Moses, W. S., Matoth, Y., and Levin, S., Sickle Cell Disease in Israel; Report of 5 Cases in an Arab Family, *Harefuah, 51,* 1956, 255-262.
177. Motulsky, A. G., Glucose-6-Phosphate-Dehydrogenase Deficiency Haemolytic Disease of the Newborn and Malaria, *Lancet, ii,* 1961, 1168.
178. Moualem, F., and Matoth, Y., Thalassemia in a Non-Kurdi Iraqi Jewish Family, *Dapim Refuiim,* 1962. (In press.)
179. Mourant, A. E., Kopeć, A. C., and Domaniewska-Sobczak, K., *The ABO Blood Groups: Comprehensive Tables and Maps of World Distribution,* Blackwell Scientific Publications, Oxford, 1958.
180. Nathan, H., The Skeletal Material from Nahal Hever. Cave No. 8—"The Cave of Horror," *Atiqot, J. Isr. Dept. Antiquit., 3,* 1961, 165-175.
181. Nathan, H., Expedition to the Judean Desert 1960. The Skeletons of the Nahal Mishmar Caves, *Israel Explor. J., 11,* 1961, 65-69.
182. Neel, J. V., A Study of Major Congenital Defects in Japanese Infants, *Am. J. Human Gen., 10,* 1958, 398-445.
183. Nelken, L., Occurrence of Diabetes Mellitus in the Different Population Groups in Jerusalem (Hebrew), *Dapim Refuiim, 14,* 1955, 293.
184. Nelken, L., Incidence of Diabetes in Jews from Yemen (Hebrew), *Dapim Refuiim, 17,* 1958, 250-251.
185. Nowell, P. C., and Hungerford, D. A., Chromosome Studies in Human Leukemia. II. Chronic Granulocytic Leukemia, *J. Nat. Cancer Inst., 27,* 1961, 1013-1038.
186. Oldham, P. D., Pickering, G., Roberts, J. A. F., and Sowry, G. S. C., The Nature of Essential Hypertension, *Lancet, i,* 1960, 1085-1093.
187. Ortar, G., Verbal and Performance Tests: Their Relative Value as Tools for Intercultural Comparison (Hebrew), *Megamot, 9,* 1958, 207-227.
188. Payne, R., and Hackel, E., Inheritance of Human Leukocyte Antigens, *Am. J. Human Gen., 13,* 1961, 306-319.
189. Payne, R., and Rolfs, M. R., Fetomaternal Leukocyte Incompatibility, *J. Clin. Invest., 37,* 1958, 1756-1763.
190. Penrose, L. S., Measurements of Pleiotropic Effects in Phenylketonuria, *Ann. Eug.,* London, *16,* 1951, 134-141.
191. Penrose, L. S., Genetical Causes of Malformation and the Search for their Origins, in *Ciba Foundation Symposium on Congenital Malformations,* Churchill, London, 1960, pp. 22-31.
192. Platt, R., The Nature of Essential Hypertension, *Lancet, ii,* 1959, 55-57.
193. Price Evans, D. A., Manley, K. A., and McKusick, V. A., Genetic Control of Isoniazid Metabolism in Man, *Brit. Med. J., 2,* 1960, 485-491.
194. Rachmilewitz, M., and Grossowicz, N., Anemia in Pregnancy, *Proceedings of the III Congress of Internal Medicine,* Uppsala, Sweden, 1956, 540-545.
195. Rachmilewitz, M., Izak, G., Grossowicz, N., Aronovitch, J., Sadowsky, A., and Bercovici, B., Anemia in Pregnancy, *Harefuah, 57,* 1959, 81-85.
196. Ramot, B., Ashkenazi, I., Rimon, A., Adam, A., and Sheba, Ch., Activation of Glucose-6-Phosphate Dehydrogenase of Enzyme-Deficient Subjects. II. Properties of the Activator and the Activation Re-

action, *J. Clin. Invest., 40,* 1961, 611-616.
197. Ramot, B., Fischer, S., Szeinberg, A., Adam, A., Sheba, Ch., and Gafni, D., A Study of Subjects with Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency, II. Investigation of Leukocyte Enzymes, *J. Clin. Invest., 38,* 1959, 2234-2237.
198. Ramot, B., Fisher, S., Remez, P., Schneerson, R., Kahane, D., Ager, J. A. M., and Lehmann, H., Haemoglobin O in an Arab Family, *Brit. Med. J., 2,* 1960, 1262-1264.
199. Ramot, B., Sheba, Ch., Fisher, S., Ager, J. A., and Lehmann, H., Haemoglobin H Disease with Persistent Haemoglobin "Bart's" in an Oriental Jewess and her Daughter, *Brit. Med. J., 2,* 1959, 1228-1230.
200. Ramot, B., Sheba, Ch., Adam, A., and Ashkenazi, I., Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficient Subjects: Enzyme-Level in Saliva, *Nature, 185,* 1960, 931.
201. Ramot, B., Szeinberg, A., Adam, A., Sheba, Ch., and Gafni, D., A Study of Subjects with Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency: Investigation of Platelets Enzyme, *J. Clin. Invest., 38,* 1959, 1659-1661.
202. Ramot, B., Duvdevani-Zirkert, P., and Tauman, G., Distribution of Haptoglobin Types in Israel, *Nature, 192,* 1961, 765-766.
203. Ramot, B., Duvdevani-Zirkert, P., and Kende, G., Haptoglobin and Transferrin Types in Israel, *Ann. Human Gen.,* London, *25,* 1962, 267-271.
204. Reitler, R., and Yoffe, J., Filariasis in the Jewish Communities of Malabar, *Acta Med. Orient., XIV,* 1955, 83-95.
205. Rife, D. C., *The Distribution of the Blood Groups,* Blackwell, Oxford, 1953.
206. Rimon, A., Ashkenazi, I., Ramot, B., and Sheba, Ch., Activation of Glucose-6-Phosphate Dehydrogenase of Enzyme Deficient Subjects: I. Activation by Stroma of Normal Erythrocytes, *Biochem. and Biophys. Res. Comm., 2,* 1960, 138-141.
207. Rood, van, J. J., Leeuwen, van, A., and Eernisse, J. G., Leucocyte Antibodies in Sera of Pregnant Women, *Vox. Sang. (N.S.), 4,* 1959, 427-444.
208. Sachs, L., and Bat-Miriam, M., The Genetics of Jewish Populations. I. Finger Print Patterns in Jewish Populations in Israel, *Am. J. Human Gen., 9,* 1957, 117-126.
209. Sadovsky, A., De Vries, A., and Bercovici, B., Anemia in Pregnancy, *Acta Med. Orient., 14,* 1955, 67-71.
210. Sakada, I., Personal Communications, 1960.
211. Sandbank, U., Tryfus, H., and Katzuni, E., Oxalosis in Two Brothers (Hebrew), *Harefuah, 60,* 1961, 213-218.
212. Sandberg, A. A., Ishihara, T., Miwa, T., and Hauschka, T. S., The In Vivo Chromosome Constitution of Marrow from 34 Human Leukemias and 60 Non-leukemic Controls, *Cancer Res., 21,* 1961, 678-689.
213. Schieber, C., Target-Cell Anaemia: Two Cases in Bucharan Jews, *Lancet, ii,* 1945, 851-852.
214. Scowen, E. F., Watts, R. W. E., and Hall, E. G., Further Observation on the Genetic Basis of Primary Hyperoxaluria, *Ann. Human Gen.,* London, *23,* 1959, 367-381.
215. Seedorff, K. S., *Osteogenesis Imperfecta. A Study of Clinical Features and Heredity based on 55 Danish Families Comprising 150 Affected Persons,* Ejnar Munksgaard, Copenhagen, 1949.
216. Selander, P., The Frequency of

Cystic Fibrosis of the Pancreas in Sweden, *Acta paediat., 51,* 1962, 65-67.
217. Ser, J., Essential Pentosuria (Hebrew), *Dapim Refuiim, 20,* 1961, 2-12.
218. Sheba, Ch., Ashkenazi, I., and Szeinberg, A., Taste Sensitivity to Phenylthiourea among the Jewish Population Groups in Israel, *Am. J. Human Gen., 14,* 1962, 44-50.
219. Shepard, T. H., Lee, L. W., and Krebs, E. G., Primary Hyperoxaluria, II. Genetic Studies in a Family, *Pediatrics, 25,* 1960, 869-871.
220. Shields, J., and Slater, E., An Investigation into the Children of Cousins, *Acta Genet. Stat. Med., 6,* 1956 60-79.
221. Simmons, J. S., Whayne, T. F., Anderson, G. W., and Horack, H. M., *Global Epidemiology. A Geography of Disease and Sanitation,* Lippincott, London, 1954.
222. Siniscalco, M., Bernini, E., Latte, B., and Motulsky, A. G., Favism and Thalassemia in Sardinia and their Relationship to Malaria, *Nature, 190,* 1961, 1179-1180.
223. Siniscalco, M., Motulsky, A. G., Latte, B., and Bernini, L., Indagini genetiche sulla predisposizione al favismo.—II. Dati familiari. Associazione genica con il daltonismo, *R. Accad. Naz. Lincei,* Ser. VIII, *28,* fasc. 6, 1960, 1-7.
224. Siwe, S., The Reticulo-Endotheliloses in Children, *Adv. Pediat., 4,* 1949, 117.
225. Slatis, H. M., and Hoene, R. E., The Effect of Consanguinity on the Distribution of Continuously Variable Characteristics, *Am. J. Human Gen., 13,* 1961, 28-31.
226. Smithies, O., Zone Electrophoresis in Starch Gels: Group Variations in the Serum Proteins of Normal Human Adults, *Biochem. J., 61,* 1955, 629-641.
227. Smithies, O., Variations in Human Serum β-Globulins, *Nature, 180,* 1957, 1482-1483.
228. Sohar, E., Prass, M., Heller, J., and Heller, H., Genetics of Familial Mediterranean Fever (FMF), *Arch. Int. Med., 107,* 1961, 529-538.
229. Sorsby, A., *Clinical Genetics,* Butterworth, London, 1953.
230. Steinberg, A. G., Dependence of the Phenotype on Environment and Heredity, page 133 of this volume.
231. Stevenson, A. C., and Cheeseman, E. A., Heredity and Rheumatic Fever. Some Later Information about Data Collected in 1950-51, *Ann. Human Gen., 21,* 1956, 139-144.
232. Subhamani, B., Personal Communication, Ministry of Health, Thailand, 1961.
233. Sutton, H. E., Neel, J. V., Binson, G., and Zuelzer, W. W., Serum Protein Differences between Africans and Caucasians, *Nature, 178,* 1956, 1287.
234. Swinyard, C., Multiple Congenital Contractures (Arthrogryposis): Nature of the Syndrome and Hereditary Considerations, *Proceedings of the Second Conference on Human Genetics, Rome,* 1961. (In press).
235. Szabo, M. A., and Ross, L., Prevalence of Heart Disease among School Children in Israel, *J. Pediat., 49,* 1956, 417-424.
236. Szeinberg, A., Adam, A., Mayers, F., Sheba, Ch., and Ramot, B., A Hematological Survey of Industrial Workers with Enzyme Deficient Erythrocytes, *Arch. Indust. Health, 20,* 1959, 510-516.
237. Szeinberg, A., Adam, A., Ramot, B., Sheba, Ch., and Mayers, F., The Incorporation of Isotopically Labelled Glycine into Glutathione of Erythrocytes with Glucose-6-Phosphate Dehydrogenase Defi-

ciency, *Biochem. Biophys. Acta, 36,* 1959, 65-73.
238. Szeinberg, A., Asher, Y., and Sheba, Ch., Studies on Glutathione Stability in Erythrocytes of Cases with Past History of Favism or Sulfa-Drug-Induced Hemolysis, *Blood, 13,* 1958, 348-358.
239. Szeinberg, A., Bar-Or, R., and Sheba, Ch., Distribution of Isoniazid Inactivation in Various Jewish Groups in Israel, *Proceedings Second International Conference on Human Genetics, Rome,* 1961. (In press.)
240. Szeinberg, A., Kellerman, J., Adam, A., Sheba, Ch., and Ramot, B., Hemolytic Jaundice Following Aspirin Administration to a Patient with a Deficiency of Glucose-6-Phosphate Dehydrogenase in Erythrocytes, *Acta haemat., 23,* 1960, 58-64.
241. Szeinberg, A., Ramot, B., Sheba, Ch., Adam, A., Halbrecht, I., Rikover, M., Wishniewsky, S., and Rabau, E., Glutathione Metabolism in Cord and Newborn Infant Blood, *J. Clin. Invest., 37,* 1958, 1436-1441.
242. Szeinberg, A., Sheba, Ch., Hirschorn, N., and Bodonyi, E., Studies on Erythrocytes in Cases with Past History of Favism and Drug-Induced Hemolytic Anemia, *Blood, 12,* 1957, 603-613.
243. Szeinberg, A., Sheba, Ch., and Adam, A., Enzymatic Abnormality in Erythrocytes of a Population Sensitive to Vicia faba or Haemolytic Anaemia Induced by Drugs, *Nature, 181,* 1958, 1256-1258.
244. Szeinberg, A., Sheba, Ch., and Adam, A., Selective Occurrence of Glutathione Instability in Red Blood Corpuscles of the Various Jewish Tribes, *Blood, 13,* 1958, 1043-1053.
245. Szeinberg, A., Sheba, Ch., Ramot, B., and Adam, A., Differences in Hemolytic Susceptibility among Subjects with Glucose-6-Phosphate Dehydrogenase Deficiency, *Clin. Res., 8,* 1960, 18.
246. Thannhauser, S. J., *Lipidoses, Diseases of the Cellular Lipid Metabolism,* 3d ed., Grune and Stratton, N.Y., 1958.
247. Tough, I. M., Buckton, K. E., Baikie, A. G., and Court-Brown, W. M., X-Ray-Induced Chromosome Damage in Man, *Lancet, ii,* 1960, 849-851.
248. Tough, I. M., Court Brown, W. M., Baikie, A. G., Buckton, K. E., Harnden, D. G., Jacobs, P. A., King, M. J., and McBride, J. A., Cytogenic Studies in Chronic Myeloid Leukaemia Associated with Mongolism, *Lancet, i,* 1961, 411-417.
249. Touster, O., Essential Pentosuria and the Glucuronate-Xylulose Pathway, *Fed. Proc., 19,* 1960, 977-983.
250. Touster, O. J., Reynolds, V. H., and Hutcheson, R. M., The Reduction of L-Xylulose to Xylitol by Guinea Pig Liver Mitochondria, *J. Biol. Chem., 221,* 1956, 697-709.
251. Touster, O. J., and Harwell, S. O., The Isolation of L-Arabitol from Pentosuric Urine, *J. Biol. Chem., 230,* 1958, 1031-1041.
252. Ungar, H., and Laufer, A., Necropsy Survey of Atherosclerosis in the Jewish Population of Israel, *Path. Microbiol., 24,* 711-717.
253. Wahrman, J., Schaap, T., and Robinson, E., Manifold Chromosome Abnormalities in Leukaemia, *Lancet, i,* 1962, 1098-1100.
254. Waisman, H. A., Advances in the Understanding of the Metabolic Abnormalities in Phenylketonuria. Mental Retardation, in Bowman, P. W., and Mautner, H. V. (eds.),

Proceedings of the First International Medical Conference on Mental Retardation, Grune and Stratton, N.Y., 1960.

255. Walber, A. R. R., and Arvidsson, V. B., Fat Intake Serum Cholesterol Concentrations and Atherosclerosis in the South African Bantus, *J. Clin. Invest., 33,* 1954, 1358-1365.
256. Wallgren, A., Incidence of Hypertrophic Pyloric Stenosis, *Am. J. Dis. Child., 62,* 1941, 751-756.
257. Wang, H. L., Morton, N. E., and Waisman, H. A., Increased Reliability for the Determination of the Carrier State in Phenylketonuria, *Am. J. Human Gen., 13,* 1961, 255-261.
258. Weissenberg, S., Die Jemenitischen Juden, *Ztschr. Ethnologie, 41,* 1909, 307-327.
259. Weissenberg, S., Die Mesopotamischen Juden in Anthropologischer Beziehung, *Arch. Anthrop., 10,* 1910, 233-239.
260. Weissenberg, S., Zur Anthropologie der Persischen Juden, *Ztschr. Ethnologie, 45,* 1913, 108-119.
261. Wilkerson, H. L. C., and Krall, L. P., Diabetes in a New England Town, a Study of 3,516 Persons in Oxford, Mass., *J. A. M. A., 135,* 1947, 209-216.
262. Wilson, M. G., and Schweitzer, M., Pattern of Hereditary Susceptibility in Rheumatic Fever, *Circulation, 10,* 1954, 699-704.
263. Wolfsohn, T., On the Use of Certain Performance Tests in Examining Elementary School Children (Hebrew), *Megamot, 3,* 1952, 148-157.
264. Woolf, C. M., Stephens, F. E., Mulaik, D. D., and Gilbert, R. E., An Investigation of the Frequency of Consanguineous Marriages among the Mormons and Their Relatives in the United States, *Am. J. Human Gen., 8,* 1956, 236-252.
265. Wyngarden, J. B., and Elder, T. D., Primary Hyperoxaluria and Oxalosis, in Stanbury, J. B., Wyngarden, J. B., and Frederickson, D. S. (eds.), *The Metabolic Basis of Inherited Disease,* McGraw-Hill, N. Y., 1960.
266. Yadin, Y., The Expedition to the Judean Desert 1960, Expedition D. *Israel Explor. J., 11,* 1961, 36-52.
267. Yoeli, M., and Soriano, J., Public Health and Social Problems of an Indian Jewish Settlement in Israel, *Harofe Haivri, 31,* 1958, 54-72.