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RESEARCH ON HUMAN POPULATION GENETICS

Report of a WHO Scientific Group

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CONTENTS

	Page
1. Introduction	5
2. Data to be collected in studies of primitive groups	7
3. Populations suitable for investigation	18
4. Organization of field research	20
5. Equipment and other facilities	22
6. Data processing	27
7. Training of research workers	29
8. Relations of the research team with the population studied	30
Annex : WHO Reference Centres in Human Genetics	31

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ON HUMAN POPULATION GENETICS

Geneva, 3-7 July 1967

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RESEARCH ON HUMAN POPULATION GENETICS

Report of a WHO Scientific Group

A Scientific Group on Research on Human Population Genetics was held in Geneva from 3 to 7 July 1967. The meeting was opened Dr A.M.-M. Payne, Assistant Director-General, who welcomed the participants on behalf of the Director-General. He referred to the WHO Scientific Group on Research in Population Genetics of Primitive Groups, which had met in 1962 and had recognized the urgency for study of the remaining primitive populations of the world; it had recommended guidelines for the conduct of the interdisciplinary studies required.¹ Such studies were at present receiving a world-wide stimulus through the co-operation of the seven-year International Biological Programme sponsored by the International Council of Scientific Unions and supported by some fifty countries. The present meeting had been convened to give research workers engaged in such studies the opportunity of comparing their findings, discussing the problems they had encountered and, if necessary, suggesting a revised protocol for studies, taking account of recent experience.

Dr J. V. Neel was elected Chairman of the Group; Dr F. M. Salzano, Vice-Chairman; and Dr N. E. Morton and Dr R. J. Walsh, Rapporteurs.

1. INTRODUCTION

There are in the world today a certain number of communities living in conditions that may be called "primitive", in the sense that they still obtain food by means that were prevalent in the early phase of human history, such as hunting and food-gathering, nomadic pastoralism, and digging-stick-and-hoe type of agriculture.

Such groups live under conditions that approximate very closely to those that have prevailed during the greater part of man's existence. It is probable that modern man owes much of his present genetic endowment to the pressure of evolutionary forces associated with the way of life to be seen among such primitive communities.

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1964, 279.

Some of these communities are likely soon to become extinct, and many if not all are undergoing more or less rapid and substantial cultural change as a consequence of contact with more advanced societies.

The need for investigating these communities before they disappear is therefore urgent. It should also be noted that their study is of interest not only for genetic reasons; pathology, epidemiology, sociology and a variety of other disciplines can benefit greatly from studies on disappearing primitive groups. It is also worth remembering that parallel studies in these disciplines are essential for a full understanding of the genetic problems.

The following features of such populations are of particular genetic interest :

(1) morbidity, mortality and fertility patterns and their possible contributions to natural selection, especially with reference to specific genetic systems;

(2) demographic factors (geographic and age distributions, migration patterns) that affect inbreeding and genetic drift;

(3) the biological consequences of inbreeding and outcrossing;

(4) the biological consequences of formal kinship and marriage systems;

(5) the effects on these factors of contact with more advanced cultures;

(6) the discovery of hitherto unknown genes and of patterns of gene frequencies unusually favourable for study;

(7) the biological relationship of these groups to neighbouring populations or to those more remote in time or space.

The emphasis here on primitive groups by no means implies that other populations may not be equally valuable, or even more valuable for studying certain genetic problems, such as inbreeding, outbreeding or selection effects. Such populations include isolates — religious, social or geographic — within technically advanced societies; populations with high mortality; and populations undergoing rapid expansion, genetic admixture or acculturation.

There are important by-products of genetic research on primitive groups. Some of these depend on the fact that isolation, effective in keeping populations primitive, has also important epidemiological consequences; others depend on the extreme ecological conditions in which some of these groups live. Examples are :

(1) the availability of immunologically “ virgin ” populations, unexposed to certain infectious diseases;

(2) the possibility of finding unique ways of life, including diets, and their effects on important physiological characters as well as on chronic diseases;

(3) in primitive groups exposed to cultural change, the possibility of testing the effect of changing ways of life on physiological characters and on disease patterns;

(4) the likelihood of discovering unusual diseases, abnormal frequencies of rare diseases, and sometimes new disorders.

One further aspect of these studies requires stressing: all human groups benefit from them. The local population benefits directly and promptly from medical and dental attention, and eventually from the construction of normative growth and nutritional standards. Moreover, the study of their demographic and health status helps the local administrators identify those problems that most urgently require attention.

2. DATA TO BE COLLECTED IN STUDIES OF PRIMITIVE GROUPS

When designing a comprehensive study to determine the genetic structure of a population in relation to a variety of ecological and social factors, a detailed and systematic assessment should first be made of the kinds of information that will be needed. There is a tradition of comparative studies in diverse cultures in many disciplines. Field manuals, handbooks, and forms — such as those produced by WHO and by the International Biological Programme (IBP) — are available for use in studies of ecology, anthropology, demography, nutrition, growth and development, obstetrics, cardiovascular disease, cancer, immunology, etc. These will usually need adaptation for use in primitive groups and special modification for the peculiarities of the specific groups under study.

The suggestions made below are intended to improve the comparability of such studies. It is recognized that there will be few if any studies in which it will be possible to make all the observations listed, but workers will be able to select from the list those investigations applicable to their particular projects. The performance of even a small number of these investigations in a primitive population may make a valuable addition to the knowledge of the biology of that population.

2.1 Demography and socio-cultural environment

Individual records

A census should be taken, when possible, of the village investigated and village maps should be obtained to provide a frame of reference for

the individuals examined as well as to permit identification of their birthplace and current residence. All localities should be specified as precisely as possible to permit population structure analysis.

For all individuals examined, and, if possible, for temporary absentees and recent emigrants, the following information should be obtained :

- (a) name of informant and relationship to subject (mother, father, other);
- (b) date and place at which record was taken;
- (c) name of subject, residence and/or social group affiliation (vernacular and alternative names should be given in standard phonetic form);
- (d) sex;
- (e) age (specifying whether recorded age, estimated age or age supplied by an informant);
- (f) birthplace (and for immigrants date and manner of entry into community);
- (g) full names, birthplaces, and residences of siblings, parents, and grandparents;
- (h) mating records : husbands or wives dead, alive, divorced; place of residence; dates important for periods of marriage and cohabitation and ages of wives at menarche and menopause should also be recorded;
- (i) names of all children alive, their birthplaces and birth dates, sex, and residence, if in other villages; the alleged paternity of each child and whether it has been adopted should be carefully noted;
- (j) number of dead children by sex, birth date, age at death, and cause of death;
- (k) all available information on pregnancies terminated by stillbirth or abortion, so as to obtain as complete a record as possible of the history of pregnancies of each woman;
- (l) means of individual identification, such as photography, fingerprints, dental impressions, etc.

Collection of the data listed in (g), (h) and (i) may indicate redundancy in the records. This will be difficult to avoid entirely, but it can be greatly reduced by cross reference between individual records of husbands, wives and children.

Code numbers for individuals, written on small cards or boards to be carried and displayed by the examinees, may also facilitate the organization of the field work. In addition, use of such numbers will help to preserve the privacy of individuals.

The information listed in (g) to (i) is essential for constructing the pedigree of the group (giving the genetic paths connecting individuals

as well as their known ancestors and descendants), which should be as extensive and complete as possible. Its construction will be helped also by the verification of paternity by means of genetic data. It should be remembered that, from the genetic point of view, information is needed on : (1) degree of consanguinity of individuals; (2) fertility and mortality on a family basis; and (3) immigration, based on birthplaces of individuals and their relatives. It may be added that information on diurnal, seasonal and long-term migration of individuals and groups under study would be useful for the analysis of migration patterns. Migration between groups, when ascertainable, is of importance for the estimation of gene flow.

Social factors affecting fertility and survival

Among these are :

- (a) post-partum practices affecting the mother, child and father (residential, sexual, nutritional, social taboos, etc.);
- (b) infant feeding practices, breast feeding, weaning, etc.;
- (c) nutritional differences within and between families;
- (d) pre-marital relations between the sexes;
- (e) marriage patterns and their variants, e.g., prescribed marriage (as with mother's brother's daughter); polygamy; child marriage; divorce;
- (f) frequency of extra-marital mating;
- (g) factors involved in mating choices;
- (h) patterns of sexual intercourse; contraceptive practices; ritual mutilation of genitalia;
- (i) change in the sex ratio and differential infanticide.

2.2 Health status and disease pattern

Medical and dental surveys are needed to determine the present and past causes of mortality and morbidity, to detect the presence of genetic disorders in the population, and to evaluate the current health status of persons of all ages in the community. Information on congenital abnormalities, nutritional status, and other factors affecting reproduction is particularly valuable.

The medical survey examinations will detect only some of the diseases present in the community and should be regarded as screening procedures. For many purposes, a prevalence survey will provide useful data, especially for chronic diseases, but a longitudinal study of each specific disease is essential to an understanding of the dynamics of that disease in the community. Whatever specific diseases are detected will clearly dictate what

further medical investigations and genetic studies are needed. The examinations and procedures listed below are applicable to all individuals when making a genetic study of a primitive population; items essential for all studies are indicated by an asterisk :

- (a) individual medical history *;
- (b) physical examination * including visual acuity and ophthalmoscopy *, gynaecological, and neurological * examination; other specialized clinical examinations may be made where circumstances permit;
- (c) nutritional status *;
- (d) dental examinations *;
- (e) X-ray examination :
 - chest
 - wrist for bone age
 - teeth and other parts of skeleton where practicable (other methods for measuring bone-mineral contents are available and may be useful);
- (f) skin sensitivity testing :
 - tuberculin, including standard PPD and atypical mycobacterial tuberculins;
- (g) haematological examination :
 - complete blood count
 - examination for sickling
 - thick and thin smears for parasites;
- (h) blood specimens for biochemical, serological and genetic studies *;
- (i) urine collections :
 - routine clinical urine analysis
 - bacterial cultures as indicated;
- (j) faeces :
 - tests for occult blood
 - examination for helminths and protozoa.

The following special procedures are to be carried out only on *selected* individuals or in case of specific disease indications :

- (a) electrocardiogram, electroencephalogram, electromyogram;
- (b) pulmonary function studies (note danger of cross-transmission where infection is present);
- (c) endocrine and metabolic disease investigations (renal, hepatic, nutritional, and endocrine functions);

- (d) 24-hour urine collection for biochemical determinations, including protein electrolyte hormone analysis;
- (e) tensiometer studies for glaucoma;
- (f) sputum examination for parasites and bacteria;
- (g) microbial isolation studies;
- (h) additional skin testing : Schick tests; tests for allergens, histoplasmin, blastomycin, coccidioidin, trichinella and other antigens, as indicated;
- (i) analysis of saliva, sweat, nasal smears, cervical smears, cerebrospinal fluid;
- (j) screening tests for intermediate metabolites, such as carbohydrates, phenylpyruvic acid, uric acid, steroids, etc., may be done on serum and urine specimens as facilities permit.

2.3 Genetic and other physical data

The same four somewhat arbitrary categories are used here as in the 1964 report of the WHO Scientific Group :¹

- A. Serological and biochemical genetics.
- B. Other genetic characters.
- C. Morphology.
- D. Physiology.

The first category comprises a number of simply inherited variations that can be detected by biochemical or serological methods. The third category includes certain morphological characteristics (measurements of gross bodily size and shape) that cannot at present be genetically analysed in detail, although determined by genes to a varying extent. These are often of interest not only to geneticists but also to nutritionists, students of growth, and anthropologists concerned with the comparison of populations by traditional methods. Some of the determinations listed below may conveniently be made in the course of the medical examination.

A. SEROLOGICAL AND BIOCHEMICAL GENETICS

Tests on Blood

The decision as to what tests for red-cell groups and other inherited antigens should be done on a particular series of specimens depends

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1964, 279.

almost entirely upon the availability of the various reagent antisera; world supplies of some of these antisera are extremely small (see section 5.1). The main limiting factor for enzyme tests is the cost of the reagent, while the availability of adequate space and staff is an important consideration both for enzyme tests and for tests for serum groups.

I. Red cells

(a) Blood group antigens

Genetic system	All series	Selected series	Series specially selected as justifying the use of very rare reagents
ABO	A A ₁ B H	s S ^u He Mj ^a Vw	St ^a M ^s
MNSs	M N S		P P ^k
P	P ₁		C ^u C ^x CE E ^u e ^s e ^l
Rh	C D D ^u E c e	C ^w Ce f(cc) V(cc ^s) E ^w	
Lutheran		Lu ^a Lu ^b	
Kell	K	k Kp ^a Js ^a	Kp ^b Js ^b
Lewis	Le ^a Le ^b		
Duffy	Fy ^a	Fy ^b	
Kidd		Jk ^a	Jk ^b
Diego		Di ^a	Di ^b
Wright		Wr ^a	
Auberger			Au ^a
Xg			Xg ^a
Yt			Yt ^a Yt ^b
Dombrock			Do ^a
Cost			Cs ^a

(b) Enzymes

All series

Glucose-6-phosphate dehydrogenase
6-phosphogluconate dehydrogenase
Lactate dehydrogenase
Acid phosphatase
Adenylate kinase
Phosphoglucomutase
C₅ esterase

Selected series

Catalase
Leucine aminopeptidase
Hexokinase
Carbonic anhydrase
Malic dehydrogenase

(c) Haemoglobins

All series

Haemoglobin variants and allied conditions

II. Serum**(a) Serum groups***All series*

Haptoglobins
 Transferrins
 Group-specific components (Gc)
 Globulin allotypes such as Gm, Inv, Isf

Selected series

Low-density lipoproteins including Ag,
 Lp and Ap groups

(b) Enzymes*All series*

Pseudocholesterase

(c) Antibodies*All series*

Routine screening for blood group antibodies, including tests with control cells from populations being examined. In many cases, it may be desirable to carry out tests for auto-immune antibodies at this stage.

Tests on Saliva*All series*

Secretor status ABH
 Secretor status Le^a and Le^b

Selected series

Titration of A, B, H
 Titration of Le^a and Le^b

Tests on Urine*Selected series*

Amino-acid patterns including β -aminoisobutyric acid

Tests of possible future importance but still under development

Antigens of platelets and leucocytes and other histocompatibility antigens
 Isoniazid acetylation
 Whole blood amino-acid pattern

B. OTHER GENETIC CHARACTERS**Cytogenetic Studies**

Buccal smears may be examined for sex-chromatin in some cases, and blood cell and skin biopsy cultures for determination of karyotypes are desirable on selected subjects.

Colour Blindness

This should be recorded using Ishihara or other charts and, if possible, with a precision instrument, such as the anomaloscope.

Ability to Taste Phenylthiocarbamide (PTC)

Solution sorting tests should be used.

Other Possibly Genetic Traits

There are several easily observed traits that possibly have a genetic basis, although it has not been conclusively demonstrated in all cases. They include direction of hair whorl; handedness; finger formula; toe formula; degree of thumb hyperextensibility; hand clasp; arm fold; tongue roll; tongue fold; ear cerumen.

C. MORPHOLOGY

Measurements of Body Dimensions

The following should be included:¹

(a) *Weight*

(b) *Linear measurements:*

<i>Cranial</i>	<i>Postcranial</i>
maximum length	total height
maximum breadth	sitting height
minimum frontal diameter	biacromial breadth
bizygomatic breadth	chest breadth
total face height	chest depth
nose height	bi-iliac breadth
nose breadth	buttocks-knee length
ear length	tibial height
ear breadth	shoulder-elbow
upper face height	elbow-middle finger
bigonial diameter	bicondylar humeral breadth
	wrist breadth
	wrist a-p diameter
	knee breadth
	ankle breadth

} optional

} optional

¹ Other anthropometric measurements will be needed for special studies.

(c) Circumferential measurements

head	forearm	} optional
mid-upper arm (at level of skin fold measurement)	wrist	
	ankle	
chest		
abdomen (umbilical level)		
calf		

(d) Measurement of skin folds

triceps	mid-axillary	} optional
subscapular	iliac	

(e) Standardized photographs

Three views of total body : front, side, back
 Two close-ups of head and face : front, profile

Optional : colour photographs of selected subjects for correlation with reflectance spectrophotometric observations and skin biopsies.

Anthroposcopic Observations

Useful features to observe are : hair (amount, texture, form, presence at various sites); eyefold; eyebrow thickness; brow-ridge prominence; chin eminence; lips; nose; ear (size, lobe attachment, helix). Most of these can be rated from photographs; they should be rated by the same observer using, where appropriate, a five-point scale (absent, small, +, ++, +++), based on a defined midpoint.

Studies on Pigmentation

(a) Skin. Measurements should be taken by reflectance spectrophotometry on the medial surface of the upper arm, the flexor surface of the forearm, the forehead, and preferably on the chest and buttock as well. Observations should be made half-an-hour to one hour after washing the area with alcohol.

(b) Hair. Observations should be made of colour, texture, form, and grayness, the last separately for head, beard and body. Where possible, samples of hair should be collected and then studied by reflectance spectrophotometry.

(c) Eyes. For most of the populations listed in section 3, eye colour is not likely to be of significance. If required, approximate records can be obtained with a standard scale.

Dental Studies

These should include direct observation and scoring of the following : eruption and development, fissural patterns and cusp numbers, periodontal status, and occlusion. These observations should be supplemented by casts and radiographs. Dental pathology and genetic variation should also be recorded.

Dermatoglyphics

Digital and palmar prints should be obtained ; in special cases, prints of the toes and the sole may also be useful.

D. PHYSIOLOGY

The personnel, equipment and time generally available will not be sufficient to permit extensive physiological studies, but they should be considered in certain instances and are essential for many projects of the International Biological Programme.

The situation in a given group will determine the nature of the physiological investigations most appropriate : nutritional assessment, physical performance capacity, adaptation to cold and heat, endocrine and cardiorespiratory function, neurological co-ordination, etc.

E. PSYCHOMOTOR PERFORMANCE AND BEHAVIOURAL STUDIES

Owing to the complexity of these studies and the special peculiarities of each field situation, investigators should consult with experimental psychologists and other behavioural scientists before proceeding to field work. Cinema recording of behaviour is to be recommended and telemetric methods of following activity patterns are now feasible.

2.4 Data on physical and biological environment

To complement the genetic investigation of a group, a reasonably detailed ecological study is desirable. This will vary in scope according to the resources available, but every attempt should be made to obtain the collaboration of well-trained biologists and physical scientists. Data from such studies often provide valuable information on the exploitation of the environment by the people under study.

Important fields of study include :¹

Climatological and geological studies

- (a) Standard meteorological observation with attention to micro-climatology
- (b) Soil survey
- (c) Geological and topographical survey, aerial photographs of terrain
- (d) Cartography.

Botanical studies

- (a) An ethnobotanical survey, including cultivated and gathered foods, medicinal plants, psychoactive drugs, vegetable body paints, etc.
- (b) Yield studies and nutritional evaluation of food plants
- (c) Habitat survey : types and distribution of cover.

Zoological studies

- (a) An ethnozoological survey, including domestic animals and their diseases, parasitic organisms and animal food resources, etc.
- (b) Nutritional analysis of animal foods
- (c) A medical entomological survey
- (d) An ecological survey of local fauna.

2.5 Archaeological data, oral tradition and historical records

Data of this kind are important to an understanding of the demographic and genetic composition of the group and its population history. Sources of such information are :

- (a) The recollections of the subjects studied, and those of shamans or elderly informants.

The oral tradition of disease epidemics, famines, raids and wars, floods, typhoons, volcanic eruptions, earthquakes, and other disasters, fissions and fusions of villages, visitors, and other events influencing social and genetic structure should be recorded. The oral tradition of neighbouring groups concerning such events may also be of importance.

¹ The list that follows is a slightly modified version of the one given in the WHO Scientific Group report : *Wld Hlth Org. techn. Rep. Ser.*, 1964, 279.

(b) Outside observers, e.g., government officials, traders, missionaries, and local medical personnel, as well as regional and area medical records, etc.

Medical data on epidemics and disease pattern for the surrounding populations will of be great importance.

(c) Archaeological investigation, including examination of dead bodies — skeletal and dental remains or tissues naturally preserved by desiccation, freezing or chemical action.

3. POPULATIONS SUITABLE FOR INVESTIGATION

Some populations suitable for study are set out below under the five broad regional headings : (a) the Arctic, (b) South America, (c) Africa, (d) Asia, and (e) Australasia (including South Pacific islands).

In each area, a few populations are mentioned that offer special opportunities. No attempt is made to be exhaustive or to suggest priorities, which will differ from case to case and investigator to investigator.

(a) *The Arctic*

In Greenland, the Angmagssalik, Upernivik, and Polar Eskimo; in Canada, the Igloolik, Cumberland Sound and Frobisher Bay Eskimo; in Alaska, the Wainwright, Kodiak, and St Lawrence Eskimo, and the Pribilof Islanders; in Scandinavia and the USSR, the Lapps; in the USSR, the Chukchi and the Eskimos. Some of the preceding populations are already under study.

(b) *South America*

Some of the groups mentioned in the 1964 WHO Scientific Group report are being studied, notably the Guayaki (Paraguay), Ayoréo or Moro (Paraguay, Bolivia), Kayapo (Brazil), Waika or Yanomamo (Brazil, Venezuela); further research among these groups is highly desirable.

In addition, at least 200 other groups, including the Siriono of Bolivia, Tiryio, Jivaro, Bari (Motilonos Bravos) should be considered.

(c) *Africa*

Northern Africa : the Tedah of the Tibesti Mountains; Sudanese groups; and, further south, the Touareg.

Central Africa : work is in progress among the Babinga Pygmies and should be extended to the neighbouring Pygmies as well as to the "Bushmanoid" peoples.

East Africa : in connexion with Hadza studies under way, the following neighbouring groups should be examined : the Isanzo and the Sukuma (Bantu agriculturists); the Mangati (pastoralists); the Sandawe; and the Ethiopian Highlanders.

South and Southwest Africa: the Bergdamara, Hottentots, Bushmen, Batwa, and Rehoboth Basters (a hybrid group).

West Africa : the Dogon. The Bedik, Coniagui, Bassarri, and Badya-nanké are at present under study.

(d) *Asia*

In South-East Asia : the Yumbri of northern Thailand; the Semang in South Thailand and Malaya; Punan and Penan groups in Borneo; Negritos, including the Batak and Mamanua, in the Philippines; and perhaps some "Kubu" groups in Indonesia (Sumatra and adjacent islands). There are also more than sixty groups of primitive agriculturists and several groups of "boat people" (Moken, Bajau) in South-East Asia that warrant study as populations of genetic interest.

Study of the Ainu of Hokkaido and Sakhalin, and of the Taiwan aborigines should be extended.

In India, the hunter-gatherers of the Andaman Islands (Onge, Jarawa, Juwai, and Sentinelese), deserve special attention. Other populations of interest include the Veddah of Ceylon, and, in India, the Chenchu, Kadar, Irula, Warli, Katkari, Paliyan, Koya-Dora, and Reddi.

(e) *Australasia (including South Pacific islands)*

Australian aborigines in Arnhem Land, who retain their original way of life, will be studied by the Australian Committee of the IBP. Those in the Western Desert remain for study.

New Guinea continues to offer a great number of groups for genetic study. Those now under investigation in Eastern New Guinea include the Fore and other groups in the kuru disease region, surrounding Eastern Highland groups, the Kukukuku and groups in the Markham Valley, Maprik and Jimmi River Valley. In West Irian (West New Guinea) the Dani and the inland Asmat and Auyu peoples of the southern coastal plain are under investigation. The Sentani Lake people have been extensively studied. Groups near Medang and Goroka will be intensively studied by the United Kingdom and Australian Committees of the IBP.

Work has begun among the Mortlock and Manus Islanders of the Australian Territory of Papua and New Guinea as well as on certain groups in New Britain, New Ireland, Buka and Bougainville Islands. In the British Solomons, some work has been done on Malaita, on Rennell and Bellona, and on Tikopia Islands. The Tongariki, Banks and Torres Islanders of the New Hebrides will be followed biomedically. In Micro-

nesia, work is in progress on most of the Western Caroline and Mariana Islands, including Guam. The Polynesian people on Kapingamaringi and Nukuroru Islands are being investigated.

Many opportunities remain throughout Oceania. Groups being resettled (Tikopians on the Russell Islands, Gilbert and Ellice Islanders on Guadalcanal, and Nauru Islanders) can throw light on the interactions between environment and genetics and on the effects of migration.

4. ORGANIZATION OF FIELD RESEARCH

Much of the previous work on primitive groups has failed to provide medical, demographic, genealogical, or anthropological data adequate for comprehensive studies of the kind recommended above. Such studies involve the collaboration of many different specialists for varying periods and require field work in relatively inaccessible parts of the world. They demand careful attention in planning and execution.

The guide for the organization of population genetic studies in primitive populations set out in the 1964 WHO Scientific Group report¹ was considered by the meeting to be generally satisfactory. As noted in that report, however, "No single scheme . . . will necessarily apply to every population listed. For some groups, for instance among the Eskimo populations of the Arctic or the aborigines of Australia, sufficient detailed knowledge of the cultural, linguistic, health and genetic structures is available already. For these, it will be possible to plan in detail a full investigation without either preliminary investigations or pilot studies."

The suggestions below for the various stages of comprehensive studies in new areas are reproduced, with slight modifications, from the 1964 report.

4.1 Preparatory studies

(a) Contact with the appropriate departments of the government in whose territory the population resides. This should be followed by establishing the most suitable channels of communication with administrative officers in the areas concerned.

(b) Contact with scientific personnel with previous or current experience of the population concerned.

(c) Collection of a complete bibliography and survey of relevant museum material.

(d) Formation of a group of experts to provide a nucleus of persons who will collaborate in the later stages of the project. This should include

¹ *Wld Hlth Org. techn. Rep. Ser.*, 1964, **279**, 19.

at least a human geneticist, medical scientist, social or cultural anthropologist, and a physical anthropologist.

(e) A preliminary visit to the area by one member of the group, who will have long-term association with it, to establish personal contact and understanding with local administrative officials and the actual population. The subjects and their community leaders should be informed of the nature of the investigations and approval obtained from them. At this stage, the degree of linguistic contact must be assessed and an appraisal made of transport facilities and health hazards in the area of study.

4.2 Pilot studies

Work will usually be facilitated if the cultural or social anthropologist working with the project starts his work in the community at least several months in advance of the arrival of other workers. His early presence should be utilized for organizing housing and working facilities, transport, interpreters, etc. He should be on hand for the arrival of the further members of the pilot teams : at least two persons from the group of specialists working on the project, with suitable supporting personnel. At least one of these specialists should, if possible, be a physician.

4.3 Full-scale studies

In addition to the human geneticist, medical scientist, cultural or social anthropologist, and physical anthropologist, certain other experts will need to visit the area for varying periods of time. These may include the appropriate specialists in linguistics, dentistry, geography, ecology, geology, archaeology, zoology, botany, ornithology, medical entomology and agricultural science, as well as whatever medical specialists can be recruited. Such studies will often extend for long periods, and may require repeated visits to the area, either to verify or to amplify previous observations.

Again, the time and effort required cannot be specified precisely. However, a full-scale study of the kind envisaged will probably require four field workers continuously for two years. In addition, provision should be made for one person to remain in the field for a further year to maintain contact with the group and facilitate repetition of some of the observations if necessary.

In organizing a full-scale study, attention must be given to the schedule of arrival and departure of investigators, in particular to the appropriate synchronization of visits (e.g., the presence of zoologists and medical entomologists in the area at the same time); to transport arrangements, both for personnel and for specimens; and to assuring the co-operation

of base laboratories. This last point is no less important than the others. No comprehensive study can be successful unless prior assurances are received that the material collected can be processed both accurately and expeditiously.

4.4 Follow-up studies

Although it is often impossible to guarantee sufficient financial support to enable a research programme to be continued for several years, it is important to realize that much valuable information can be collected from follow-up studies. Organizers of these studies should be aware that it is advisable to secure the collaboration of appropriate specialists in the study of each disease found or suspected of being an important factor in the lives of the people studied.

5. EQUIPMENT AND OTHER FACILITIES

For comprehensive studies of the kind described in the preceding sections, specialized facilities and equipment will be needed. In some areas, these are already available, but in others suitable facilities will have to be established or the existing services will have to be expanded. Adequate funds for this purpose must therefore be provided.

In addition to routine equipment, such special items as microwave radio transceivers, electricity generators, and portable X-ray equipment will be required. High priority must be given to specialized forms of transport, including boats and outboard motors, 4-wheel-drive vehicles and aircraft.

Special attention will also have to be given to the following problems :

5.1 Supply of reagents

The main limiting factor in most of the tests for the red cell groups and for other inherited antigens present in the blood is the shortage of reagents. Most of the latter are obtainable only as sera from persons who have become immunized to the antigens in question; consequently, the total world supply is strictly limited. It may prove possible to prepare a few of the reagents through animal immunization and from plant extracts; research directed to increasing the supply from these sources should be encouraged.

At the same time, attempts should be made to obtain voluntary donations of blood from suitably immunized persons in all parts of the world, and to ensure the most economical distribution of the sera. At

present, rare antisera are either sold through commercial channels or are distributed by individual investigators to others on a personal basis. A world pool of rare antisera would be of help. However, the main shortage will be relieved only if reagents can be made in the laboratory. Probably the most promising way of doing this is by lymphocyte culture, but this development is unlikely to come for several years.

5.2 Reference samples

To ensure comparability of results between different laboratories carrying out tests for hereditary blood factors, it is necessary that control samples of blood, or the appropriate part of the blood, containing each of the factors in question, should be widely available. This is especially important for the rarer factors and for antigens that require rare diagnostic reagents.

It is desirable that suitable control samples should be preserved, preferably in liquid nitrogen, at a small number of centres, under the control of an international organization. Use should be made of the relevant WHO Reference Centres (see Annex, p. 31).

5.3 Collection, transport and storage of specimens

Most of the difficulties and disasters that affect population surveys of blood factors occur in the field rather than in the laboratory. Methods of collection and transport can be divided into two main categories — those to be used with ordinary refrigeration and those to be used with liquid nitrogen.

5.3.1 *Methods using ordinary refrigeration*

Ideally, specimens should be taken by venepuncture by a closed method into a sterile container, which should be refrigerated within a few hours to $+4^{\circ}\text{C}$ and transmitted within three days to the testing laboratory. The main causes of deterioration are :

(a) Prolonged keeping without refrigeration, either immediately after collection or during transportation (this is, of course, especially deleterious in the tropics);

(b) Lack of sterility — usually due to collection in or transfer to an open container;

(c) Freezing solid (transport in unheated part of aircraft; more rarely erroneous use of solid carbon dioxide or storage in deep freeze).

Because they allow several specimens to be taken from a single venepuncture by a closed method, Vacutainers or other similar tubes are

particularly suitable for field use. Plastic bags can also be used for this purpose, taking blood through one needle, which is connected successively to a number of bags. The tubes or bags should not be opened until they reach the testing laboratory.

For many purposes, 10-ml Vacutainers with 0.1 ml of 30% potassium edetate¹ will serve. When red cell enzyme studies are to be undertaken, or when a short delay in transport is expected, the use of 1.5 ml of acid-citrate-dextrose (ACD) solution per 10 ml of blood should be considered.

If serum or plasma has to be separated from a blood specimen in a Vacutainer, it should be drawn directly into a second Vacutainer, a separate needle being inserted as an air inlet.

Each glass should have a serial number scratched on it with a diamond; plastic bags should have a preprinted serial number. This is the nearest that can be devised to a disaster-proof identification system, the need for which has repeatedly been shown when some, or even all, the specimens from an expedition have been unidentifiable on arrival (e.g., owing to the labels having been washed off by melting ice).

Specimens should be packed in insulated containers. These may be thermos flasks, but expanded polystyrene boxes insulate almost as well and are much lighter and more convenient. Ice should be enclosed in a bag of stout polyethylene and, if the journey has to be a long one, provision made for its renewal (preferably by substituting another ready-frozen container). Only in quite exceptional cases is it justified to collect specimens more than one day's travel from a road head.²

The following ready printed stick-on and untearable tie-on labels should be taken with the expedition :

(a) Labels addressed to the receiving laboratory, including its phone number and instructions to phone on arrival at the home airport;

(b) Striking red labels bearing the words : "Blood samples — Urgent — Fragile";

¹ Potassium salt of ethylenediamine tetra-acetic acid.

² It is usually important that only a single airline should handle specimens, as long and disastrous delays have been found to occur at interchange airports. Therefore, a member of the expedition staff should personally hand over specimens to an official of the airline on which the main transport of the specimens is to be undertaken, even if this means that he has to travel with the specimens on a local airline. Alternatively, one member of the expedition staff could hand the specimens to the local airline and a second member supervise the interchange. Such precautions are expensive, but their neglect has at times led to the serious deterioration of most of the specimens collected by an expedition, with a loss of thousands of dollars. In addition, it is necessary to make detailed preliminary arrangements with a senior official at the transmitting airport, preferably the airport manager. It is also necessary to make special arrangements to ensure in advance the prompt delivery of specimens to the receiving laboratory, except in the case of airlines known by experience to have efficient arrangements for delivery.

(c) Labels with instructions on care of specimen : " Blood samples in fragile glass tubes. Cool on ice or in refrigerator at + 4°C to + 10°C. DO NOT FREEZE. Do not place in unheated part of airplane. Do not allow to rewarm".

Any person accompanying specimens to the airport should carry clearly written and obviously authoritative instructions as to their care, both for his own reference and to show to officials.

The testing laboratory should have a cablegram address and one should if possible also be arranged for the expedition in the field. A prearranged code for cables may also be useful. When specimens are sent off, a cablegram should be sent to the testing laboratory specifying the flight number, the number of specimens, and if necessary, their nature. The laboratory should report back the date of receipt, condition of specimens and, if necessary, instructions for remedying errors in collection or transport. All field records and letters should be written in duplicate books so that one copy is sent to the laboratory and one retained in the field. It is best to make lists of specimens in triplicate, one to be sent with the specimens, one separately by airmail, and one to be retained in the field.

Detailed written instructions should be prepared and given to collectors for reference in time of doubt. These should explain standard methods of collection, cooling, storage and transportation, with an account of problems likely to be encountered in different situations and suggestions as to how they might be overcome.

5.3.2 *The use of liquid nitrogen during transport*

No method that is satisfactory in all respects is at present available. In the past, reliance has been placed largely on the method of Huntsman et al.¹ using polyvinylpyrrolidone (PVP) as an additive. This gives good results both with red cell antigens and with enzymes when the whole procedure is carried out in the laboratory, but with specimens collected in the field difficulties have invariably arisen in tests for the red cell antigens, especially in the antiglobulin test, and in some cases, but not all, there has been a deterioration of enzymes.

More tests of different methods should be carried out in the laboratory, and, depending on the results obtained, further extensive experimental collections should be made in the field by an experienced laboratory worker with some knowledge of field conditions, in order to establish the best additive to use and the most efficient way of using it. In addition

¹ Huntsman, R. G., Hurn, B. A. L., Ikin, E. W., Lehmann, H. & Liddell, J. (1964) *Transfusion*, 4, 354.

to the PVP-method, the glycerol method or some modification of it should be tried.¹ For such work the support of an international organization would be required.

5.3.3 Long-term storage in liquid nitrogen

The original method of storing small samples of intact red cells in liquid nitrogen is now routinely used for the maintenance of reference panels of red cells. Subsequently, methods using PVP, dimethylsulfoxide (DMSO) and glycerol were devised and are used in various laboratories for the conservation of red cells, white cells, etc. The use of liquid nitrogen storage depends upon the development of reliable methods of freezing and thawing adapted to the purposes in view.

The experience of the past 10 years leads to the confident belief that, once such methods have been perfected, it will be possible to store biological materials without appreciable deterioration for periods of the order of fifty years. As a result, such materials as red cells, white cells, fibroblasts and even whole tissues will be available in fresh condition many years after they have been collected. Thus, detection of all genetic markers will still be possible many years after an expedition has collected the specimens.

This makes it worth while to consider the possibility of setting up regional storage facilities with a comprehensive recording and retrieval system.

5.4 Testing laboratories

It is desirable that the major international centres and WHO reference laboratories be encouraged by the provision of additional financial support to extend their testing facilities.

Further, the staff of local laboratories in developing countries should receive training from visiting scientists so that more extensive laboratory investigations can be undertaken locally; the reference laboratories should be used primarily for more detailed characterization. The laboratory facilities required for haemoglobin work and for glucose-6-phosphate dehydrogenase testing are considered in the reports of two WHO Scientific Groups.²

Work on the red-cell enzymes has been developed rather rapidly in a small number of biochemical laboratories which are interested more in their biochemistry and formal genetics than in population surveys.

¹ Krijnen H. W., et al. (1964) *Vox Sang. (Basel)*, **9**, 559-572.

² *Wld Hlth Org. techn. Rep. Ser.*, 1966, **338**; 1967, **366**.

Only a very few laboratories throughout the world are able to undertake comprehensive enzyme surveys, and their capacity is strictly limited. Some surveys have been undertaken by splitting specimens between several laboratories, each doing tests for one or a few systems. Such "specimen splitting", which also affects systems other than enzymes, can introduce very serious delays in the final publication of results.

The position with regard to haptoglobins, transferrins and Gc-groups is somewhat similar, though probably rather more laboratories are doing limited population surveys.

Further consideration is therefore needed in regard to both the setting up or expansion of laboratories able to undertake large-scale enzyme work and the methodology of processing results obtained by several laboratories during a single survey.

5.5 Facilities for the international transport of biological specimens

Much damage to blood specimens has in the past been caused by delays in transport at international frontiers and by lack of facilities during transit through intermediate countries on the journey. It is highly desirable that governments should provide or approve special facilities for the rapid transit of perishable biological specimens, such as blood, through and between their countries, and that such facilities should be made known both to research workers and to the officials with whom they have to deal.

It is recommended that WHO study the agreements already in existence for facilitating the transport of biological samples through and between countries and encourage further agreement on this question. It is suggested that in view of the importance of these agreements to the IBP, this should be done in consultation with the International Council of Scientific Unions.

6. DATA PROCESSING

A wide variety of data-processing services and facilities are needed. It is noted that the greater part of the data obtained from studies of primitive groups are processed at relatively few centres, and that the greatest need is not so much for the acquisition of better computer facilities as for the wider availability of existing computer programmes and wider appreciation of their potential. Moreover, in considering the available facilities, electromechanical equipment should not be overlooked.

Computer programmes may be considered under three heads :

- (a) general statistical programmes;

(b) service programmes of special relevance to the genetics of primitive groups; and

(c) other service programmes.

(a) *General statistical programmes*

General statistical programmes are available at computer centres, and it was felt to be outside the terms of reference of the Group to attempt to collate them.

(b) *Service programmes of special relevance to the genetics of primitive groups*

There is demand for the following types of service programme :

(1) *Demographic tabulation and analysis*: tabulation from population data of fertility, mortality, morbidity, longevity and other items of demographic interest; analysis of migration patterns.

(2) *Genealogical tabulation and analysis*: Construction of genealogies from demographic, and possibly ultimately genetic, information; calculation of inbreeding and other coefficients; provision for interrogating stored genealogical data; the automatic drawing of genealogies; automatic consistency checks; and collation with demographic information.

(3) *Segregation analysis* : analysis of genetic segregation, and testing for inconsistencies due to wrongly ascribed paternity or recording errors.

(4) *Gene-frequency estimation* : efficient estimation of gene frequencies from samples of related and unrelated individuals; general parameter estimation.

(5) *Phylogenetic analysis* : testing for heterogeneity in gene frequencies; calculation of genetic distances between populations, and distance based on anthropometric and other data; automatic construction and drawing of phylogenies and gene-distribution maps.

Most of the above programmes already exist, sometimes in several versions, and it is recommended that steps be taken to ensure that :

(1) there is no duplication of effort, and that where programmes with the same function exist, they are critically compared;

(2) standards exist for the preparation of data intended for computer analysis;

(3) arrangements be made for the circulation of information about the function and availability of programmes and programming services in the above fields;

(4) access to computer programmes and facilities is made available to investigators;

(5) the training of geneticists in data-processing techniques is facilitated;

(6) a standard programming language is adopted.

Aims (1) to (5) could best be achieved by the designation and support of regional computing centres prepared to accept visitors wishing to take advantage of their programmes and computer facilities, and by the establishment of an information exchange service on computer programmes and facilities.

It is assumed that in most cases no funds, or only nominal funds, would be needed for computer rental. However, support for the visits of investigators, for programming, and for the training of geneticists in data-processing, would be required. The designation of regional centres by WHO would ensure their co-operation in the provision of computer time and, in addition, would encourage a high level of competence and interest in the areas of research covered by a particular centre. It is recommended that WHO consider designating such centres.

It is suggested that FORTRAN IV be adopted as the standard programming language, other FORTRAN variants being used where FORTRAN IV is locally unavailable.

(c) Other service programmes

In some instances there may be a need for other programmes, such as those for estimating genetic linkage, for automatic karyotype analysis, and for record linking. These have been developed in a number of specialized centres, from which advice may be obtained when required.

7. TRAINING OF RESEARCH WORKERS

There is a general shortage of technical personnel, particularly of human geneticists, serologists, nutritionists, social anthropologists and linguists, for the multidisciplinary studies envisaged. It is recommended that WHO, within its fellowship and training grant programme, provide for the training and international exchange of students in these various fields; special efforts should be made to advertise the availability of these opportunities. It is further suggested that the Special Committee for the IBP should be requested to make available through its regular channels information on relevant short technical courses that are arranged from time to time by the various institutions.

8. RELATIONS OF THE RESEARCH TEAM WITH THE POPULATION STUDIED¹

Any research team has ethical obligations to the population under study. The investigator should always be bound by the legal and ethical considerations governing the conduct of medical and biological research workers. It is essential that harmonious relations be maintained both during and after each research visit. From previous field experience, the following factors have been found to be especially important.

(a) The privacy and dignity of the individual must be respected at all times and the anonymity of subjects must be maintained in publications. The comfort and individuality of subjects must be safeguarded, e.g., some people are unwilling to queue, or to have others present during examination or questioning. Care should be taken that individuals do not undergo an excessive number of examinations at any one time.

(b) Satisfactory reward should be provided for the subject's participation in the research and for any services provided. The nature of the recompense should receive careful consideration. The advice of local authorities may be invaluable, both on this question and in general, so as to avoid giving offence through ignorance of local customs.

(c) The local population should benefit from such studies by the provision of medical, dental and related services.

(d) The maintenance of congenial social relationships will be enhanced by methods suitable to particular areas, e.g., eating with families on occasion, exchange of information.

(e) All groups have learned individuals, e.g., experts on oral traditions and those with systematized knowledge and interpretations of natural phenomena. Consultation and exchange of information with such persons will often be of immediate value to ensure good relations and lead to the appreciation of the achievements of such peoples. Such information is pertinent to their cultural and therefore biological history.

(f) There should be the utmost regard for the cultural integrity of every group. All possible measures should be taken to prevent the activities and presence of the research team from adversely influencing the cultural continuity of the population being studied.

¹ This section is reprinted with slight modifications from *Wld Hlth Org. techn. Rep. Ser.*, 1964, 279, 24.

Annex

WHO REFERENCE CENTRES IN HUMAN GENETICS

A network of international and regional reference centres has been established by WHO with the aim of promoting the use of specific standards, in materials and in methodology, and of developing research and collaboration on problems arising from the reference work of the centres. Such centres can make an important contribution to investigations in human genetics, particularly those requiring the identification of antigenic variants on the surface of cells or of biochemical variants in human tissues and body fluids.

The following centres have been designated in fields relating to the subject matter of this report :

WHO International Blood Group Reference Laboratory

Medical Research Council's Blood Group Reference Laboratory, Lister
Institute of Preventive Medicine, London, England

*WHO International Reference Centre for Genetic Factors of Human
Immunoglobulins*

Centre départemental de transfusion sanguine et de génétique humaine,
Rouen, France

*WHO Regional Reference Centres for Genetic Factors of Human
Immunoglobulins*

Department of Medical Microbiology, University of Lund, Sweden
Department of Biology, Western Reserve University, Cleveland, Ohio,
USA

WHO International Reference Centre for Abnormal Haemoglobins

Medical Research Council's Abnormal Haemoglobin Research Unit,
Department of Biochemistry, University of Cambridge, England

WHO International Reference Centre for Serum Protein Groups

Zoology Department, University of Texas, Austin, USA

*WHO International Reference Centre for Glucose-6-Phosphate Dehydro-
genase*

Department of Medicine — Medical Genetics, University of Washington,
Seattle, Wash., USA

WHO Regional Reference Centres for Glucose-6-Phosphate Dehydrogenase

Department of Haematology, Tel-Hashomer Government Hospital,
Israel

Sub-department of Haematology, University College Hospital, Ibadan,
Nigeria
