Medical genetics around the world

Medical genetics in South Africa

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Medical practice in South Africa is firmly grounded in the British tradition. The country's first medical faculty was established at the South African College (soon to become the University of Cape Town) in 1917 and, although the second followed in Johannesburg three years later, another 23 years were to elapse before another came into being. Today there are seven medical schools (eight if one includes the small, recently established one at Umtata in Transkei, one of the 'independent' homeland states), which, between them, produce some 900 doctors each year.

Before 1918 South Africans went to British medical schools to train, although preclinical courses were offered at the South African College from 1911. Many of the country's medical academics have pursued specialist training in the United Kingdom, with smaller numbers proceeding to the USA or Holland for postgraduate studies. There are approximately 20 000 registered doctors in South Africa (95% are white and 85% are male) and the doctor:population ratio was 1:1344 in 1985 (up from 1:2157 in 1960), which compares with 1:650 in the UK, 1:520 in the USA, and 1:10 500 in Kenya. (For these and the following statistics relating to medical practice in South Africa I am indebted to Kirsch and Benatar.¹) In the major urban areas of South Africa the ratio is 1:875 but in the 'homelands' (rural areas inhabited almost exclusively by black people) it is much less favourable. In Transkei it is 1:19 000 and in Qwa Qwa, another of South Africa's national states, it is 1:116 000. In the 1940s the ratio of general practitioners to specialists was 7:1, but the figure has gradually fallen until it is now 3:1. In western Europe the ratio is 1:1. Successful completion of a six year course and a one year internship makes the candidate eligible for

registration as a general practitioner. Specialisation requires four to five years of recognised training and passing an examination.

Medical genetics is not a recognised speciality and the handful of South African medical geneticists are specialists in internal medicine, paediatrics, or pathology, who have subsequently undergone further training as geneticists either in South Africa or in the USA. There may be a need for medical genetics to become a recognised speciality in South Africa, but until more academic departments are brought into being this is unlikely to occur. Medical scientists with PhD degrees in biological subjects can register with the South African Medical and Dental Council (the equivalent of the General Medical Council in the United Kingdom) as Medical Natural Scientists. One is head of a university medical genetics department and others are in administrative positions with the Department of National Health and Population Development (DNHPD) Genetic Services Division.

Tertiary health care is of a high standard; the academic hospitals have the full range of sub-specialities and 'high-tech' medicine is as much in evidence in these hospitals as it is in the teaching hospitals of Europe and North America. There is considerable debate within the profession about the appropriateness of much of this training because, in the first place, large numbers of the medical graduates leave the country within a few years of qualifying and, secondly, a large proportion of the population (more than 50%) lives in rural areas, and there is a reluctance on the part of doctors to work in these relatively remote areas.

The infant mortality rates (IMRs) (death occurring within the first year of life per 1000 births) in South Africa averaged over 1981 to 1985 are 12.3 for white, 17.9 for Indian, 51.9 for 'Coloured' (or mixed peoples), and 94 to 124 for African populations.² The figure for Africans can be broken down to show a value of 25.6 for those resident in Soweto and 130 for those in the Transkei; the IMR for 'Coloureds' shows a 2.6 times higher rate in rural compared with urban areas. The commonest causes of death in the 1 to 12

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month age group were related to poor environmental and socioeconomic circumstances, that is, infections, gastroenteritis, and measles, followed by respiratory illness, ill defined causes, and nutritional disorders. For whites in the same age group the causes are congenital abnormalities, respiratory disease, accidents, and ill defined causes.

The underprivileged (largely black) population lack many of the basic necessities of life and, as a consequence, suffer from the spectrum of ill health and disease typical of the third world: high infant mortality rates, infectious diseases, diseases of malnutrition, and the effects of trauma. The contrast with the diseases of the privileged (largely white) population is striking; among the latter are to be found health statistics little different from those in Europe and the USA, with low infant mortality rates and with cardiovascular disease and neoplasms, followed by respiratory diseases and accidents, as the main causes of death. Infectious diseases account for fewer than 16 per 100 000 deaths whereas in the black (African) and 'Coloured' populations they feature as the main causes of death.

It is not surprising, therefore, that genetic disorders should be considered to be relatively unimportant by the black community, whereas to large numbers of whites the relative importance of these disorders is clearly apparent. Nevertheless, as increasing numbers of black people enjoy improved socioeconomic status and become better educated, they too will expect, and in fact already demand, genetic services.

Although hard data are not available, it is fair to assume that admissions to paediatric wards at both the predominantly racially segregated State hospitals for white patients and the private nursing homes (many of which are open to patients of all races) conform to the patterns encountered in the hospitals of developed countries, that is, perhaps 30% of the children are admitted because of inherited or partly inherited disorders. At the hospitals for black children the proportion is considerably lower.

A lively debate is taking place in South Africa on the question of privatisation of health care delivery.³ The Government is committed to privatisation in spite of the fact that in 1985 in white designated South Africa (that is, the country excluding the homelands and 'independent' states), only 8% of blacks (that is, the people who are not white) belonged to medical health insurance schemes compared with 72% of whites. In the homelands the proportion of blacks belonging to medical aid schemes must be nearly zero. On the face of it, the percentage of the gross national product (GNP) allocated to health seems reasonable, ranging from 4.5% to 5.2% between 1976 and 1984. Nearly half of the sum is, however, spent in the private sector and this is to provide health for the affluent (largely white) minority, constituting less than 20% of the total population. Most western

countries spend an average of between 7% and 11% of the GNP on health care, although WHO claims that 5% is a reasonable figure for a developing country. The GNP has been increasing in many countries over recent years, whereas in South Africa the increase has been negligible.⁴

It is difficult to calculate how much money is spent on the prevention of disease in South Africa but the Government estimates that 4.7% of public expenditure on health care (or about 2.3% of total health care expenditure) is used for prevention.⁵ The budget of the Genetic Services Division of the DNHPD for 1983/84 was R501 000, for 1984/85 it was R605 000, and by 1986/87 it had doubled to R1.3 million (about £300 000), although this large increase is almost entirely the result of the transfer of the haemolytic disease of the newborn prevention programme to Genetic Services (with the necessary funds). It had nearly doubled again by 1989/90 (DNHPD Annual Reports). These figures, however, represented only about 0.04% of the DNHPD's expenditure on health. The Provincial authorities are responsible for the provision of curative health care and do, of course, provide care for patients with genetic disorders; some of the Provincial authorities do not, however, see themselves as responsible for providing genetic counselling clinics. Most medical aid schemes contribute to the costs of prenatal diagnostic tests, including laboratory investigations, for their members. The DNHPD Genetic Services, with its small budget, has tried to encourage the setting up of clinics in centres where the medical schools have not established them, but they are few and far between and inadequate to cater for the needs of white patients/clients; it has, as yet, hardly begun to provide them for the black communities. However, if one considers that barely 50% of children are fully immunised for measles, poliomyelitis, diphtheria, pertussis, tetanus, and tuberculosis, then the 'prevention' of inherited disorders cannot be accorded a high priority rating. In 1984, for example, 14 892 cases of measles were notified with 1095 registered deaths.⁶

The history of medical/human genetics in South Africa

Although medical/human genetics is a relatively young discipline, there have been individual South African scientists, most of them medical graduates, who have pursued research in the field. The pioneering studies of Pirie,⁷ Pijper,⁸⁻¹⁰ Elsdon-Dew,^{11,12} Shapiro,¹³ and Zoutendyk *et al*^{14,15} on the blood groups of the local populations, of Klempman¹⁶ and Wilton¹⁷ on cytogenetic disorders, and of Dean¹⁸ on porphyria are noteworthy.

The relatively brief stays of Francis Galton in South West Africa, now Namibia, in 1851¹⁹ and Lancelot Hogben in Cape Town, 1927-1930,²⁰ were important

periods in the research careers of the two men and Hogben inspired psychiatrist Lewis Hurst to research the genetics of the psychoses in South Africa and, under Franz Kallman, in New York City.²¹ There has been speculation that Galton's travels among the Khoi (formerly 'Hottentot'), Nama and Dama people of Namibia were as influential on his subsequent development as was the voyage of the *Beagle* on Darwin's.²²

Any discussion of the history of medical genetics in a particular country must consider the influence which the eugenics movement might have exerted. The Eugenics and Genetics Standing Committee of the South African Association for the Advancement of Science was set up in 1920 with H B Fantham, Professor of Zoology at the University of the Witwatersrand (Wits), as its President.²³ This Committee popularised eugenic views and its members lectured on eugenics at the universities and to Eugenics Study Circles around the country. Fantham was an enthusiastic eugenicist who enjoyed close ties with the Eugenics Society of the UK. He published articles^{24 25} which he distributed to members of the Senate and Parliament, as well as magistrates and educational authorities. The Eugenics Committee condemned both mixing between racial groups and mixing between members of the same racial group who had different potentialities.²³ Appropriate marriage laws and compulsory sterilisation were to be used to prevent the birth of children suffering from hereditary mental diseases, "feeble-mindedness", "degenerate alcoholism", and "marked criminal tendencies". The South African government did not respond to the pleadings of the Committee and went no further than to recommend voluntary sterilisation.

Hogben, when he worked in Cape Town and afterwards when he held appointments in England, was a vigorous opponent of the eugenics movement,²⁶ and after Fantham left Wits in 1932 to take up a position in Canada, all references to the Eugenics Committee in the *South African Journal of Science* ceased.²³ It had become evident that the eugenics movement, with its emphasis on social stratification based on biology, would not gain support from the large Afrikaans speaking 'poor white' population, who, in addition to the blacks, would have been the chief 'victims' of any eugenics programme.

Genetic counselling was offered to small numbers of patients in the 1950s and 1960s by individual physicians interested in medical genetics (Tobias, Hurst, and Anderson in Johannesburg; Gordon in Cape Town). In a brief but useful discussion on the history of human genetics in South Africa, Hurst has claimed that human genetics "came of age in 1956 with the foundation of the South African Genetics Society".²¹ When the Society held its First National Congress in 1958 there were 70 members in attendance, including some human geneticists. For a few years

Hurst, with the help of a younger colleague, ran a Clinical Genetics Unit at the Johannesburg General Hospital, seeing three to four cases for counselling each month.²¹

In May 1962 the first Conference on Human and Clinical Genetics ever to be held in South Africa took place in Johannesburg, organised by the Wits Students' Medical Council. An impressive array of papers was presented and the young, dynamic Phillip Tobias, Professor of Anatomy and Graduate Chairman of the Conference Committee, pointed out in his opening address that the conference was a pioneering venture, taking place less than six years after the First International Congress of Human Genetics.²⁷ There were interesting contributions on human cytogenetics, biochemical genetics, blood groups, malignancy, and radiation effects. A number of genetic disorders which had particular relevance to South Africa were also discussed and all the papers were published in two issues of the Wits medical students' journal *The Leech*. Among the disorders discussed were porphyria,²⁸ muscular dystrophy,²⁹ Huntington's chorea,³⁰ red cell enzyme defects,³¹ and the haemoglobinopathies.³²

Tobias, who had completed a PhD in cytogenetics in 1952 and had set up his counselling clinic in 1956 after a visit to J V Neel at Ann Arbor, Michigan, appealed at this Conference for the inclusion of medical genetics in the curriculum for medical students and pointed to the existence in South Africa of a number of distinct populations, each posing a set of genetical questions which would be challenging to the researcher.²⁷ A year later, Tobias was able to address a plenary session of the 44th Congress of the South African Medical Association (the late J A Fraser Roberts was an invited speaker at the Congress) on the topic of genetics in medical education.³³ He pleaded for South African medical schools to institute formal tuition in human and medical genetics in the preclinical and clinical years, respectively. He envisaged that the responsibility for this teaching would initially devolve upon one or two genetics enthusiasts who might be sent to more advanced centres in Europe or North America for specialised training and experience. In fact, soon after that, two South African physicians did proceed overseas for postgraduate work in medical genetics but, unfortunately, one returned for only a few years before emigrating to work in Denmark and then Canada and the other returned but soon moved into private practice.

The enthusiasts did their best to encourage human and medical genetics and in 1972 the University of Cape Town created a Department of Human Genetics and P Beighton was appointed to the headship; his background was medicine with a strong interest in inherited connective tissue disorders including skeletal dysplasias. When the Chair of Human Genetics was created at Wits in 1975, T Jenkins was

appointed the first incumbent; his background was population genetics and haematology. At this time, the Head of the Department of Obstetrics and Gynaecology at the University of Stellenbosch was Professor W A Van Niekerk, a cytogeneticist who had studied a large series of black patients with true hermaphroditism³⁴; Van Niekerk was ably assisted in this work by a PhD cytogeneticist, A E Retief. After the move of Dr Van Niekerk to national politics (he was for some years Minister of National Health and Population Development), Retief was appointed Head of the laboratory which was later expanded into a Division and then a Department of Human Genetics. Another medical school, that of the University of Pretoria, created a Department of Human Genetics in 1989, with a paediatrician (G Gericke) as Head, and there are one or two enthusiasts at the other three medical schools.

Genetic diversity and disease

The population of South Africa (including the 10 'Homelands', four of which have gained 'independence' from the Central Government) is estimated to be 33.6 million, consisting of 74% black, 15% white, 8.5% 'coloured' or mixed, and 2.5% Asian.¹

When the Dutch established a refreshment station at the Cape of Good Hope in 1652 the indigenous peoples encountered by them were San (formerly called 'Bushmen') and Khoikhoi (formerly called 'Hottentot') who pursued a life of hunting/gathering and pastoralism, respectively. These indigenous people were decimated by epidemics of infectious disease, and most of the survivors were taken into slavery. As the immigrants moved eastwards and northwards over the next 100 years or so they encountered the black people, Bantu speaking Negroes, with whom they made treaties and fought many battles.³⁵

The population growth of the European settlers at the Cape was dramatic. By 1672 the 'white' population numbered only 168 and, although just over 200 Huguenot immigrants joined the settlement in 1688, the population numbered only 1265 by 1701. With very little immigration in the succeeding 100 years, the rapid population increase was almost entirely the result of the natural increase of this small, healthy, and fertile population. By the end of the century it had reached 15 000. The Afrikaans population (the descendants of the Dutch/German/French immigrants), during a period of about 300 years, underwent something like a 2500-fold increase, over a period, incidentally, in which Britain's population increase was about sixfold.¹⁸

It is not surprising, therefore, that the Afrikaans population should possess, in high frequency, a number of disease genes owing to founder effect. Variegate porphyria was the first to be described,¹⁸ but others have since been discovered and they are

listed in table 1, together with inherited conditions which have either high or low relative frequencies in the other populations of South Africa. It should be emphasised that not all of these claims are based on sound epidemiological studies. When studies have been carried out references are given, but when no reference is given one is relying to a large extent on general impressions.

Immigration from European countries, chiefly Britain, in the 19th century would not have significantly reduced the frequencies of these genes in the Afrikaans population by a dilution effect. There was minimal integration with the Dutch settlers and the numbers were small; of the 36 000 immigrants who arrived from the United Kingdom before 1869, for example, only half remained. English speakers account for about 40% of the total white population of today. Small numbers of Germans immigrated in the first half of the century and, between 1880 and 1910, 40 000 Ashkenazi Jews came to South Africa from eastern Europe; today the latter number 110 000, with over 60% resident in the Johannesburg area. There are about 1 million South Africans of Asiatic Indian origin, descendants of people who came to the country from 1860 onwards; the majority are Hindus who had been indentured to work in the sugar cane fields of Natal and they came from Calcutta, Madras, and Bombay. The Muslim Indians came largely from Gujerat and constitute about 20% of the Asiatic population as a whole, although in the Johannesburg-Witwatersrand area nearly 50% are Muslims. An inverted Y chromosome polymorphism exists in the latter population and 30% of 72 males showed the inversion.⁵⁹ This is probably indicative of the limited area of origin of this population in India.

The so-called 'Coloured' people are the descendants of Khoisans, Europeans, and slaves from west Africa, Mozambique, and Malaya. The Bantu speakers belong to the sub-Saharan peoples of Africa (approximately 400 million people with close genetic affinities) and the 200 or so Bantu languages, which are thought to have diverged from one another over the past 2000 to 3000 years, are now considered to have striking similarities with the Sudanic languages spoken by west Africans.⁶⁹ Based on linguistic evidence, it is claimed that the Bantu speakers arose in Central Africa and migrated east as well as south. It is of interest that the sickle cell trait is virtually absent from the South African chiefdoms with the exception of the most northerly and, perhaps, the most recent immigrants to the area, the Venda of the northern Transvaal. The mildly deficient G6PD A variant is found at frequencies between 10% and 20% while the (deficient) G6PD A⁻ variant has a frequency of less than 5% in all populations with the exception of the Venda, where it has a frequency of 10%. We have offered an explanation for the distribution of these three malaria protective traits.^{38 39}

Table 1 Inherited conditions of unusual prevalence among some southern African populations.

Population	Relatively high prevalence	Relatively low prevalence
Negro	Oculocutaneous albinism ³⁶ Hereditary intestinal lactase deficiency ³⁷ G6PD A variant ³⁸ α thalassaemia 2 ³⁹ E ₁ ^s (pseudocholinesterase deficiency) ⁴⁰ Osteogenesis imperfecta type III ⁴¹ Galactosaemia Polydactyly ⁴²	Cystic fibrosis G6PD deficiency (A ⁻) ³⁸ Sickle cell anaemia ³⁸ Phenylketonuria E ₁ ^a (pseudocholinesterase variant) ⁴⁰ Osteogenesis imperfecta type I ⁴¹ Huntington's disease ⁴³
Caucasoid Afrikaans	Porphyria variegata ¹⁸ Lipoid proteinosis ⁴⁴ Sclerosteosis ⁴⁵ Oudtshoorn skin disease ⁴⁶ Familial hypercholesterolaemia ⁴⁷ Progressive familial heart block type I ⁴⁸ type II ⁴⁸ Cystic fibrosis (Namibia) ⁴⁹ Colonic polyposis (Gardner's syndrome) ⁵⁰ Huntington's disease ⁴³ Myotonic dystrophy ^{51 52} Spondyloepimetaphyseal dysplasia with joint laxity ⁵³ Fanconi anaemia ⁵⁴ Autosomal recessive polycystic kidney disease ⁵⁵ Gaucher's disease ⁵⁶	Phenylketonuria ⁵⁷
Indian	β^0 and β^+ thalassaemia ⁵⁸ α thalassaemia 2 Sickle cell anaemia G6PD deficiency (B ⁻) Diabetes mellitus (type II) Inverted Y chromosome (in Gujarati Muslims) ⁵⁹	
Jewish (Ashkenazim)	Tay-Sachs disease ⁶⁰ Gaucher's disease ⁶¹ Niemann-Pick disease type A Pentosuria ⁶² Hereditary intestinal lactase deficiency ³⁷ Familial hypercholesterolaemia ⁶³	Dysautonomia Dystonia musculorum deformans Bloom's syndrome (not a single case found)
Mediterranean (Greeks and Italians)	β thalassaemia ⁶⁴ $\delta\beta$ thalassaemia ⁶⁴ G6PD deficiency (B ⁻) ⁶⁴	
'Coloured' (mixed)	Porphyria variegata Lipoid proteinosis ⁶⁵ Juvenile Huntington's disease ⁴³	
Multifactorial conditions Negro	Twinning ⁴² Hydrocephalus ⁴²	Anencephaly ⁴² Spina bifida ⁴² Cleft lip and cleft palate ⁴² Talipes equinovarus ⁴² Congenital dislocation of hip
Caucasoid	Talipes equinovarus ⁶⁶	Anencephaly ⁴² Spina bifida ⁴²
'Coloured' (mixed)	Cleft lip and palate ^{67 68}	

Hitzeroth and Bender⁷⁰ also studied the distribution of G6PD deficiency in the light of the malaria hypothesis and Hitzeroth⁷¹ has summarised the results of his own and other studies and used them to explain the interrelationships of South African Negroes. Studies on the distribution of HLA types in the various populations were initiated in the 1970s^{72 73} and these have been continued and expanded by du Toit in Cape Town.⁷⁴

The surviving San peoples (approximately 50 000 live in Botswana, Namibia, and southern Angola)

have no sickling, no G6PD A⁻, and very low (2%) frequencies of G6PD A, suggesting that they and their ancestors have not lived in hyperendemic malarial areas for millennia. Another malaria protective trait (the Fy allele, responsible for no Fy(a) or Fy(b) production, in the Duffy blood group system), which has virtually 100% frequency in west and central Africa, has a frequency of up to about 40% in the San and higher frequencies, reaching 90%, in some of the Bantu speaking chiefdoms of southern Africa. The frequencies of Fy^a in the latter correlate with the

proportion of San admixture in them.³⁸ Homozygosity for Fy confers resistance to *P vivax* malaria infection.⁷⁵

By using recombinant DNA technology it has been shown that the sickle haemoglobin mutation present in the Bantu speaking people of southern Africa is probably the same as that in the people of the Central African Republic who represent the northernmost distribution of the Bantu speakers, thereby providing the first proof for the biological unity of the Bantu speaking peoples.⁷⁶ An estimate of the frequency of α thalassaemia has also been made possible using molecular techniques and the α thal 2 or ($-\alpha$) mutation has been shown to have a frequency of 0.20 in the Venda and considerably lower frequencies in the other chiefdoms.⁷⁷

Research in medical genetics

More than R4 billion (approximately £1 billion) was spent on health in 1986/87 in South Africa,⁷⁸ but only about R25m was allocated by the State to the Medical Research Council (MRC) for the purpose of encouraging and supporting medical research.⁷⁹ This figure has been increasing at the rate of about 10 to 15% per annum, barely compensating for inflation, which has been running at about 15% per annum for the past several years. The actual amounts distributed for research were approximately R12m in 1984, R16m in 1985 and 1986, and R21m in 1987.⁸⁰ The MRC is not the only source of research funds, although the amounts coming to medical research from other sources like the universities, the South African Institute for Medical Research, and charitable bodies must be relatively small; there is no strong tradition of philanthropy and there is no Ford Foundation or Howard Hughes Medical Institute in South Africa! The MRC funds support research institutes staffed by full time researchers (30%) as well as Units (25%), and so-called short term researchers (15%).⁸⁰ The units are also supported by a host institution (usually a university) and the researchers are usually on the staff of these institutions. Because of their not inconsiderable teaching and service commitments they are, in effect, part time researchers. In fact, in 1986 the MRC employed or supported only 102 full time research workers. It is claimed that of the total monies used to support research and development, only 6% is allocated to medical research.⁸¹ Data for 1985 show that less than 1% of South Africa's GNP is spent on research and development, compared with over 2% in European countries like France and the United Kingdom. In the USA, Japan, and West Germany the figure is nearer 3%. When expressed as research man years per 10 000 workers, South Africa scores at 9.8, compared with 32.8 in the UK, 63.2 in Japan, and 67.4 in the USA.^{82 83}

The MRC categorises its research efforts into 20 or

so groups (called work communities) according to general fields of interest. For example, all researchers (full and part timers) working on human genetics will constitute one work community called *Human and New Genetics*. In the field of medical genetics there are MRC supported research units at the Universities of Stellenbosch (Cytogenetics), Cape Town (Inherited Skeletal Disorders), and Witwatersrand (Human Ecogenetics) and a number of short term researchers at many of the universities who are performing human genetics research are supported by Council. Another work community is concerned with *Applied Molecular Biology* and it is obvious that many of the projects encompassed in this grouping will have direct relevance to medical genetics. Included in this work community is the Centre for Molecular and Cellular Biology sited at Stellenbosch University. These two work communities received, between them, R2.5m (about £500 000) for 1989, R2.3m for 1988, and R2.3m for 1987.⁸⁰

Larger sums of money are allocated for research into subjects which most would agree are more relevant to the immediate needs of the country as a whole. Work communities all receiving significantly more funding than *Human and New Genetics* include: *Parasites and Vectors*, *Microbiology*, *Nutrition and Environmental Health*, and *Toxicology*. South Africa is a developing country, in the economic and socio-political sense, and yet the universities, including the medical schools, have prepared their graduates largely as though for work in a developed country. The trend towards increased specialisation is clearly apparent: the GP:specialist ratio of 7:1 which existed in 1940 had become 3:1 by 1989, but it is still higher than the 1:1 ratio in the USA and the United Kingdom.¹ Large numbers of South African graduates, particularly those from the Universities of Cape Town and Witwatersrand, have left the country to employ their not inconsiderable skills, talents, and expertise in the United Kingdom, North America, or Australia, and also Israel and New Zealand.

Those who remain in the country and enter research tend, however, to be attracted to the sorts of problems that challenge research workers in the developed countries of the western world and neglect those on their own doorstep. With more appropriate training, it could be argued, young South African scientists will come to accept that it is in Africa that their opportunities for research will be found:

"Our profits will come from claims worked here, not by imitating overseas work on academic problems or those unrelated to local needs, for which we lack the motivation, the intellectual climate, the financial support, and in any case usually must start too late to compete on equal terms with overseas workers".⁸⁴

Oettle, a cancer epidemiologist of world fame, was

born and educated in South Africa and, in his short life (he died in 1967 at the age of 47 years), made important contributions to medical science. He was intellectually capable of taking his place in any scientific community but he chose to devote his later research efforts to finding out why certain cancers occurred at unusual frequencies in particular southern African populations. Others, equally brilliant medical scientists, have left because of an interest in a newly emerging field (Dr Sydney Brenner and Sir Aaron Klug are outstanding examples) and the inevitable lack in South Africa of other interested colleagues, who could help create the 'community' of scientists considered by Kuhn⁸⁵ to be essential for a new scientific discipline to develop.

Brenner told Judson⁸⁶ that the South Africa of the early 1950s "was a very underdeveloped country, scientifically—a provincial country. We didn't have PhDs; facilities for research were quite primitive. I mean, if you wanted to stain something, you first *synthesized the dye*". Brenner had begun independent research on chromosomes at the University of the Witwatersrand, teaching himself out of books and "building his own centrifuge". He moved to Oxford in 1952 where he worked on phage with Sir Cyril Hinshelwood and was well placed to make a pilgrimage to the Cavendish Laboratory, Cambridge, in late April or early May 1953 to see and pay his respects to the DNA model constructed by Watson and Crick. Friendships developed and although Brenner returned to South Africa in 1955, it was only a matter of time (two years in fact) before he left again, this time for Cambridge and the MRC Molecular Biology Laboratory where he has made many important contributions to the field. During these two years at the University of the Witwatersrand, he set up a laboratory in which he did phage research but "the intellectual isolation was painful and South African politics oppressive; a fortnight after reaching Johannesburg, he wrote to a friend at Cold Spring Harbor, 'It is worse here than I ever imagined in my most terrible nightmares. The whole country just vibrates with tension.'"⁸⁶

It is evident that it was not only the 'intellectual isolation' that bothered Brenner. He had been a very politically aware student and a leader of the non-racial National Union of South African Students in 1949. The Nationalist Government had come into power in 1948 and soon passed legislation to impose its rigid segregationist policies on the country. Although the forces working on someone to leave the land of his birth are often numerous and not easy to dissect, it must be acknowledged that some have elected to emigrate for political reasons while others may have left because of the low level of remuneration in academic medicine.

Those who have succeeded in the field of human/medical genetics in their adopted countries include Martin Bobrow (now at Guy's Hospital Medical

School, London), Stan Blecher (Guelph University, Canada), Moyra Smith (UC at Irvine), Michael Hayden (Vancouver), C Legum (Tel Aviv), Denise Sher (Imperial Cancer Research Fund, London), Chris Mathew (Guy's Hospital, London), Jack Goldblatt (Perth, Australia), Anne Bowcock (Stanford), David Brock (Edinburgh), Hymie Gordon (Mayo Clinic), Maurice Super (Manchester, UK), and Michael Baraitser (Institute of Child Health, London).

Nevertheless, a number of South African scientists have, while living and working in South Africa, made impressive research contributions to the field of human/medical genetics, not all, of course, working in genetics laboratories: Beighton on connective tissue disorders, in particular the skeletal dysplasias but with numerous papers on many other clinical disorders⁸⁷⁻⁹⁴; De Wet on the biochemistry and genetics of collagen⁹⁵⁻¹⁰⁰; Retief on the human gene map and familial hypercholesterolaemia¹⁰¹⁻¹⁰⁹; Jenkins on gene mapping and population genetics¹¹⁰⁻¹¹⁸; Renee Bernstein on chromosomes and leukaemia and sex differentiation¹¹⁹⁻¹²⁵; Ralph Bernstein on red cell enzyme abnormalities^{126 127}; Bothwell on HLA linked idiopathic haemochromatosis¹²⁸⁻¹³¹; Seftel, Gevers, Berger, and Henderson on familial hypercholesterolaemia^{63 132-136}; Harley, Petersen, and Reinecke on inborn errors of metabolism¹³⁷⁻¹⁴³; and Hitzeroth on population genetics.^{70 71 144} In addition to the succession of monographs by Beighton on genetic bone diseases,¹⁴⁵⁻¹⁴⁹ deafness,¹⁵⁰ and medical history,¹⁵¹ other research volumes have been produced by South Africans on true hermaphroditism,³⁴ on Huntington's disease,⁴³ on genetics and health,¹⁵² on population genetics,¹⁵³ and on Waardenburg syndrome.¹⁵⁴ A useful book on Genetic Services has also been produced.¹⁵⁵

Genetic services

In a review of Genetic Services in the RSA, produced by the DNHPD, Pretoria, 1988, it is claimed that "Hereditary and congenital disorders are one of the major causes of infant mortality and morbidity" (the first sentence of the publication). Such a statement is undoubtedly correct for a developed population in which the IMR is of the order of 10 to 15. But when the IMR is over 25 the main causes of death are infections and nutritional diseases and not hereditary diseases or congenital abnormalities. Congenital malformations accounted for 6.9% of the infant deaths in the white population of Cape Town in 1986, for 4.5% among 'Coloureds', but only 1.1% among African blacks. The IMRs in the three populations were 9.2, 22.2, and 51.2, respectively.¹⁵⁶ Recall that the IMR is over 100 in some rural populations in South Africa and it is even 26 in Soweto.

GENETIC COUNSELLING

A recent survey has established that there are genetic

counselling clinics in most of the major centres in South Africa, 14 clinics in all.¹⁵⁷ During one year (1985), 4538 patients were seen at these clinics, with the majority drawn from the middle socioeconomic class and a marked deficiency of blacks (18% of the total). The majority (63% of patients) came from the cities in which the clinics were situated, about one third came from surrounding towns and rural areas, and 1.5% from neighbouring countries. Nearly a half were referred from hospital clinics (usually obstetrics and paediatrics) and only 14% came from general practitioners. The main indications for counselling were not very different from those in the United Kingdom¹⁵⁸; usually patients were seen only once, but in 10 to 20% of cases they were seen on two or more occasions.

These clinics are run by professionals with varying backgrounds: five are paediatricians and there are one each of a physician, haematologist, neurologist, and medical scientist/cytogeneticist. Cytogeneticists are associated with six of the clinics and genetics nurses are employed in some of them; a genetic social worker is attached to two of them. Patients are referred to appropriate support groups and appropriate pamphlets and books (national and international) are distributed. In a small number of instances patients are referred to specialist centres abroad and samples of tissue are regularly sent overseas for analysis.

The survey highlighted the need for an expansion in the staff complement in most of the clinics as well as the need for more clinics and improved laboratory facilities. Public awareness needs to be heightened and Genetic Services, Department of National Health and Population Development, needs to ensure better planning, coordination, and cooperation with the university departments and hospitals which carry the brunt of the counselling and laboratory investigations. There is a great need to extend the service so that more black, 'coloured', and Indian patients are reached. By and large, people living away from the major cities and towns are at present not reached by the service, although during 1989 40 genetic clinics were organised by Genetic Services in smaller towns in various parts of the country; many hundreds of patients "of all population groups" were seen at them (Hitzeroth, personal communication).

An analysis of the different diagnostic categories of the patients referred to a large genetic counselling clinic at the teaching hospital in Johannesburg¹⁵⁹ has shown a striking similarity with those in clinics in the United Kingdom¹⁵⁸: 23% with single gene disorders, 37% with chromosomal disorders (including those of advanced maternal age), and 13% with multifactorial disorders. This is, perhaps, not surprising because nearly all of these patients belonged to the more affluent white section of the community. An earlier larger study of the Johannesburg experience¹⁶⁰ showed that 3% of the patients presented because of

consanguinity, 2% because of teratogenic exposure in pregnancy, and 1% because of 'race classification' problems or concerns. About 700 families are referred to this clinic each year. The cytogenetics laboratory of the Department of Human Genetics, University of the Witwatersrand processes about 1600 peripheral blood samples and just over 1000 amniotic fluids for chromosome abnormalities each year. The number of amniocenteses per year seems to have levelled out at around 1050 per year, but chorionic villus sampling (CVS) is gaining in popularity and about 50 cases are done per year. In addition, a private pathology laboratory has, since 1988, been offering chromosome studies on amniotic cells and in 1989 processed 255 samples, so the number of prenatal diagnoses being carried out in Johannesburg and the surrounding areas is probably still increasing. The number of African patients undergoing amniocentesis is increasing slowly and in the period 1987 to 1989 averaged 25 per year (about 2.4% of the total number of cases) compared with seven (2.78%) in 1977, nine (1.1%) in 1984, and seven (0.7%) in 1985. Six percent of the samples investigated by the private laboratory were from African patients and 3% came from Asiatic Indians.

The Department of Human Genetics, University of Cape Town, runs regular general genetic counselling clinics at Groote Schuur Hospital (about 100 patients per year) and at the Red Cross Children's Hospital (about 450 patients); there is a large pregnancy counselling clinic (about 500 patients), a Huntington's disease clinic (about 100 patients), and an orthopaedic clinic (about 90 patients). About 400 patients are seen each year at peripheral clinics some of which are "undertaken in country areas and cater specifically for the underprivileged community" (Beighton, personal communication). The medical staff of this department comprises three full time medically qualified specialists and four part time clinicians, of whom three are specialist paediatricians with extensive genetic experience. At the invitation of the DNHPD (Genetic Services), they visit institutions for the deaf, retarded, crippled, and blind throughout the country and see over 1000 patients each year, the majority of whom are 'non-white', in an attempt to make or confirm diagnoses. Cytogenetic analyses are performed on up to 500 peripheral blood specimens and about 200 amniotic fluid samples per year. Biochemical analyses (including α fetoprotein estimations) number over 1300 per year and this number is increasing. Recently, the laboratory has added DNA testing to its armamentarium. Only 10 to 20% of the patients seen at the clinics are white and fewer than 20% of the amniotic fluids investigated for chromosome abnormalities come from white pregnancies (Beighton, personal communication). Private pathologists in Cape Town have recently introduced an amniotic cell culture service and in 1988 examined about the same number

of samples as the Department of Human Genetics. In 1989 they did a greater number. It would seem that the majority of white women in Cape Town needing amniocentesis are having the procedure and the laboratory investigations done by private practitioners.

The Department of Human Genetics at the University of Stellenbosch runs one general genetic counselling clinic per week and two specialist clinics (paediatrics and prenatal diagnosis). About 1000 patients per year are referred for counselling and cytogenetic/DNA investigations and the non-medical clinical geneticist who heads the Department is assisted by two medically qualified clinical geneticists. About 70 to 80% of the patients referred to this Department are not white (Retief, personal communications).

A paediatrician with an interest in medical genetics has, since 1972, offered counselling to patients at Addington provincial hospital in Durban, Natal. Since 1988 he has run regular clinics at hospitals for patients who are not white, including the academic hospital of the University of Natal. There are also special clinics for cystic fibrosis and spina bifida and screening programmes for β thalassaemia and hypothyroidism have been introduced (Winship, personal communication). Cytogenetic investigations are carried out at the Natal Institute of Immunology and, since 1979, this laboratory has performed maternal serum α fetoprotein testing (about 8000 per year) for a mass screening programme for the Natal Province, subsidised by the Department of National Health and Population Development (Grace, personal communication). At the Medical University of Southern Africa, near Pretoria (which includes a medical school for black students), there is a Genetic Advisory Committee which is responsible for two genetic counselling clinics per week and for the coordination of various activities concerned with a genetics service, including a cytogenetics laboratory, the investigation of specimens for biochemical disorders, and a dysmorphology or developmental clinic. The number of patients seen is now nearly 600 per year with a wide range of single gene, multifactorial, and chromosomal disorders presenting. Genetic nurses who speak the local languages assist with the counselling (Potgieter, personal communication). Before the creation of the Department of Human Genetics, University of Pretoria, small genetic counselling clinics have been run in Pretoria by a paediatrician, and in Bloemfontein they are run by a neurologist and Medical Natural Scientist. In Port Elizabeth, where there is no medical school, the Medical Director of the local Blood Transfusion Service offers a genetic counselling service, which receives considerable support from staff of the Department of Human Genetics, University of Cape Town, who see the complex cases.

Sixteen genetics nurses are employed by the Genetic Services Division, DNHPD, and they are

distributed throughout the country. They offer a wide ranging service but have expressed the general need for more genetic counselling clinics outside the main centres and closer ties with medically qualified clinical geneticists.¹⁶¹ In a recent development, Genetic Services have assigned some of these nurses to one of the academic departments of human genetics and it is hoped that this pattern of deployment will extend to other departments.

For various reasons, the Genetic Services Programme of the DNHPD has, in the main, served the 'developed' (that is, white) section of the South African population. In the first place, the meagre budget does not permit adequate numbers of counselling clinics to be set up and the staffing of the division is grossly inadequate for the task of reaching more than a fraction of the population. There is no full time medically qualified staff member in the Genetic Services Programme and the genetics nurses, who constitute the backbone of the service, have had to operate in a situation often removed from medically qualified supervisors; they have done sterling work often under difficult circumstances. Two PhD Medical Natural Scientists administer the Division of Genetic Services from an office in Pretoria and they work through Regional Directors, distributed around the country, sometimes 1000 km or more from Pretoria.

Another factor militating against the development of genetic services in the black community is the relatively poor general educational standard of this segment of the population. Only a small proportion of blacks read the glossy magazines which carry numerous articles on genetic diseases and their disruptive effects on the family. Poorly educated and poverty stricken families are very accepting of the mentally retarded child, often accepting that the birth of such a child is God's will. A child with Down's syndrome born to a black family in the rural areas will, presumably, have a shortened life expectancy because of the poor access to health care. Institutional care for the retarded black child is in short supply and the subsidies for them less than half of those provided for a white child.¹⁶²

A recent survey carried out by the National Council for Mental Health (Western Cape Forum) has established that, whereas among the white population where a little over 60% of the needs of the mentally retarded are being met, the situation among Africans is desperate, with only 8% having their needs met. If the 15 million Africans living in the 'independent' national states are included the figure drops to nearer 4%.

Although the government has neglected the health needs of the underprivileged sections of the community, individual practitioners have also not done all that they could have done to ensure a more equitable distribution of services. My own department's main

Genetic Counselling Clinic has for the 17 years of its existence been held at the 'white' teaching hospital, 20 km away from Soweto, where most of the 2 million black people of Johannesburg live. Although there is no 'apartheid' at this clinic, the geographical situation has probably contributed to the fact that fewer than 2% of the patients are black. In Johannesburg, we have accordingly made various attempts to hold clinics at hospitals for black patients. Our most recently established clinic, held each week at Baragwanath Hospital, Soweto, seems to be firmly established. Between June 1987 and December 1989 we have seen 227 families for genetic counselling at this new clinic and the range of disorders is shown in table 2. Most of the referrals were from paediatricians, in particular from those involved in neonatology, hence the preponderance of chromosomal disorders and neural tube defects which present at or soon after birth. Of the 29 mothers who gave birth to children with trisomy 21 in 1989, 11 (38%) were aged 36 years or older. This would support the view that poor contraception practices as well as late presentation for antenatal care are major problems in the black community.¹⁶³ Thirty percent of the cases suffered from single gene disorders, the larger proportion resulting from the presence of albinism, spinal muscular atrophy, and galactosaemia. The high frequency of the gene(s) for oculocutaneous albinism

in the Bantu speaking peoples of southern Africa has been well documented,³⁶ and data exist for five common birth defects (polydactyly, talipes, clefts, neural tube defects, and twins),^{42 66-68} but no epidemiological data exist, as yet, for the other conditions. A recessive form of osteogenesis imperfecta (type III) is unusually common in the African population.⁴¹ Early cases of the warfarin embryopathy syndrome were described from Baragwanath Hospital.¹⁶⁴ Its continuing commonness is the result of the high prevalence of rheumatic heart disease in Soweto and the large number of patients undergoing valve replacement surgery; continuous warfarin therapy is prescribed and many young women become pregnant while on the drug, apparently unaware of its teratogenic effects.

It is our opinion that the black patients attending the Baragwanath Hospital clinic have psychosocial needs which are very similar to those of white patients. Even the poorly educated can be helped to understand risks and some opt for prenatal diagnosis in high risk pregnancies.

SCREENING FOR GENETIC DISEASE

Neonatal screening

There is no national neonatal screening programme for phenylketonuria (PKU) in South Africa. Between 1964 and 1967 the Johannesburg City Health Department, the biggest of the country's 800 local health authorities, tested nearly 36 000 babies aged between 2 and 3 weeks and did a second test, at 6 weeks of age, on 31 000 of these, using the Phenistix method. The babies were mainly white but just under 10% were 'Coloured' or Asiatic Indians. Not a single PKU positive child was found. It has been argued elsewhere¹⁶⁵ that this study did not rule out the possibility that PKU occurs among South African whites at an incidence similar to that in other populations of European origin. However, the testing of patients at institutions for the mentally retarded has shown only a small number with PKU: two among 1568 white patients at Witrand Institution in the Transvaal¹⁶⁶ and three among 1087 white patients at a Cape Town institution.¹⁶⁷ As far as I am aware no cases of PKU have been found among the black population. Another neonatal screening programme, this time using thin layer chromatography, was instituted by Genetic Services in Pretoria in the early 1980s. After 45 600 white babies were tested without finding a single positive, the screening was discontinued in October 1986 (Genetic Services Reports, 1985 and 1986). These newborns were also tested for congenital hypothyroidism and 11 cases were discovered,¹⁶⁸ giving an incidence of 1 in 4000, similar to that in European centres and in the United States.

Hitzeroth (personal communication) has estimated that any newborn screening programme which would

Table 2 Diagnoses in 227 patients attending genetic counselling clinic, Baragwanath Hospital, Soweto, July 1987 to December 1989.

	Numbers
Chromosome disorders	67
Trisomy 21	60
Others	7
Neural tube defects	29
Anencephaly, spina bifida	24
Hydrocephalus	5
Single gene disorders	78
Osteochondrodysplasias	18
Spinal muscular atrophies	15
Oculocutaneous albinism	12
Galactosaemia	5
Epidermolysis bullosa	4
Duchenne muscular dystrophy	3
Others*	15
Multiple congenital malformations	10
Non-specific mental retardation	9
Facial clefts	5
Digital anomalies	2
Dysmorphic facies	3
Drug teratogenesis†	4
Congenital infection syndromes	2
Multiple miscarriages/infant deaths	4
Miscellaneous conditions (not genetic)	15
Normal babies	5
Total	227

*Includes one case each of the following: neurofibromatosis, tuberous sclerosis, haemophilia, factor V deficiency, thrombocytopenia-absent radius syndrome, craniosynostosis, spondylocostal dysplasia, Holt-Oram syndrome, Stickler's syndrome, Treacher-Collins syndrome, Dubowitz syndrome, Zellweger's syndrome, ichthyosis.

†One case each of fetal hydantoin and fetal alcohol syndrome and two cases of warfarin embryopathy.

include the approximately 934 000 babies (760 000 black, 83 000 mixed, 70 000 white, and 20 000 Indian) born each year would cost R3 to R4 million per year (the laboratory costs alone), but only a small fraction of this amount is at present available for laboratory investigations for the entire programme run by Genetic Services. A large proportion of the babies born to black mothers are born at home, while most black mothers who give birth in hospital are discharged by the second postnatal day. The infrastructure provided by district nurses and health visitors is virtually non-existent outside a few major urban centres, so that the follow up of positive cases is extremely difficult. This has been the experience of workers in Cape Town who, in a very recent survey, have found congenital hypothyroidism in 14 out of 62 000 white newborns (1 in 4500) and a very low prevalence among 23 200 blacks. They achieved a very poor follow up rate and unsatisfactory compliance among the black families (Bonnicci, personal communication).

From a cost-effectiveness point of view it would be sound practice to direct specific screening programmes at high risk populations. There are probably no conditions, however, which are strictly confined to one population and it would be unjust to exclude from a particular programme any person who requested the test for her child. For any programme to be successful, it is essential that the public is prepared for it by effective publicity campaigns and a level of education which ensures that they understand the benefits to be derived from the testing.

Screening the mentally retarded

The screening of patients at institutions for the mentally retarded in the Western Cape was initiated in 1972 by the Department of Human Genetics, University of Cape Town (Beighton, personal communication) and the Genetic Services Division of the DNHPD has more recently encouraged the screening of mentally retarded patients at care and rehabilitation centres, as well as the children at special schools and training centres throughout the country. There were about 8 000 mentally retarded patients in hospitals in South Africa in 1982.¹⁶⁹ Of these, approximately 5200 were in full time residential care provided by the Government. Another 2800 were cared for by subsidised or licensed institutions and special education programmes.

The screening programmes would, it was claimed, provide reliable epidemiological data and identify high risk families who could then be offered genetic counselling. Of the 1568 patients at one institution, only 20 (1.29%) had inborn errors of metabolism, a proportion no different from that in two institutions in Ireland, if one takes into account that in the latter over 2% of the patients had PKU, while in the South African case only 0.13% had PKU.¹⁶⁶

Op't Hof reports that chromosome analysis on 2054 patients at five institutions in South Africa showed 18% with abnormalities.¹⁵⁵ The Martin-Bell syndrome (MBS) has been researched by the DNHPD and cases identified in all the major population groups¹⁷⁰ and a successful prenatal diagnosis has been reported.¹⁷¹ One hundred of the estimated 1200 affected males in the country have been identified. Only 87 female carriers from the 21 families investigated were identified, leaving an estimated 1600 carrier females still to be found. In the country as a whole, there are probably 3300 females at risk of being carriers of MBS¹⁷⁰ and an enormous effort would be required to find them, especially in view of the fact that they are dispersed among all population groups and distributed far and wide in rural as well as urban areas.

Carrier detection

When Kaback initiated his whole population screening programme for Tay-Sachs disease (TSD) heterozygotes,¹⁷² local workers felt that such a programme might be introduced in South Africa where the Ashkenazi Jewish population totals 110 000, the carrier rate is about 1 in 25, and demographic and sociocultural factors were favourable. Much effort went into mobilising the community in this direction.¹⁷³ Leaders of the community, particularly the rabbis, were not enthusiastic because, it was felt, they could not publicly support a project which had as a definite component the termination of a pregnancy when an affected fetus was identified. In addition, they feared drawing attention to, and stigmatising, the Jewish community, thereby arousing 'antisemitic' feelings in a society in which 'race' features so prominently in people's attitudes and values. It was eventually agreed that the problem of TSD should be attacked by (a) alerting gynaecologist/obstetrician colleagues and encouraging them to test all their Jewish patients of child bearing age (as well as their spouses), and (b) inviting all the relatives of people who had had an affected child to come forward for testing. The Department of Health produced educational material and paid for the laboratory testing. The Southern African Inherited Disorders Association (SAIDA) was set up as a result of the efforts of a young Jewish couple who had had a child with TSD, and SAIDA has made commendable efforts to educate both the lay public and the medical profession. The Jewish communal organisations also have actively promoted awareness of the condition.

The corrected carrier rate for the TSD gene is 1 in 24⁶⁰ and by mid-1989 9269 persons had been tested and 995 carriers identified; 18 carrier/carrier marriages have been identified, 59 pregnancies monitored by amniocentesis or, more recently, chorionic villus sampling,¹⁷⁴ and eight affected fetuses aborted. In the

pretesting era at least one affected baby was born per year; we do not know of any Tach-Sachs disease baby born to the Jewish Community in South Africa since 1981.

Gaucher's disease is possibly more common among the Ashkenazi population than is TSD.⁶¹ Carrier detection is possible, but only with a more involved test procedure and with less accuracy than for TSD. High risk persons are tested in laboratories in Johannesburg and Cape Town and the spouses of carriers (in particular the obligatory carrier children of people with the disease) are also tested, thus enabling high risk pregnancies to be monitored by amniocentesis or CVS.

The haemoglobinopathies do not constitute a major problem in South Africa and sickle cell anaemia is virtually unknown in the indigenous population.³⁸ The occasional case has been found in African peoples from Mozambique, Malawi, and northern Namibia and we know of a few Indian patients. β thalassaemia also is not a major health problem and the 29 homozygous patients recently reported from Johannesburg⁵⁸ were almost equally distributed among the Indian population (15 patients) and persons of Mediterranean origin (12 Greek-Cypriot, one Portuguese, and one Italian); there was one 'Coloured' patient with β thalassaemia-Hb E disease, the Hb E doubtlessly indicative of the Malay contribution to the gene pool of this community. An earlier study found that 9.2% of the Cape Town Greek community were heterozygous for β thalassaemia.⁶⁴ The Johannesburg Indian community has been shown to have a β thalassaemia carrier rate of between 1 and 2% and a sickle cell trait rate of about 1% (Krause, personal communication).

Population screening to detect carriers of the genes for these haemoglobinopathies has not been introduced and the fact that more than 50% of the β thalassaemia patients in one study⁵⁸ were under 6 years of age indicates that babies continue to be born with the condition, in spite of the availability of prenatal diagnosis. Some Muslim couples who have given birth to an affected child have, for religious reasons, declined the abortion option in subsequent pregnancies.

After discussing the complex question of screening for disease in the South African situation, Gear¹⁷⁵ concludes that a good case can be made for screening programmes but believes that they should focus on the high risk groups. Among the 14 health problems included in his list of candidates there are only two conditions of a genetic nature: congenital hyperbilirubinaemia and fetal abnormality in utero. We would argue that other conditions, for example, congenital hypothyroidism, should be screened for but the success of such a programme would be dependent on efficient follow up and satisfactory compliance with respect to treatment. Programmes

of this nature will need to be provided by the State, otherwise those who are disadvantaged and poor will not be included.

Familial hypercholesterolaemia (FH)

The large number of FH homozygotes attending a clinic in Johannesburg in the late 1970s¹⁷⁶ drew attention to the possible high frequency of an FH allele(s) in the Afrikaans speaking white population of South Africa. A survey of plasma cholesterol levels in young adults confirmed this hypothesis and it was found that between 1 in 60 and 1 in 100 of the population was heterozygous for FH.⁴⁷ It seems likely that FH contributes significantly to the high incidence of coronary heart disease in South African 'whites' between the ages of 25 and 34 years, as the figure in males is 23.1 per 100 000 per annum, twice that of comparable North Americans.¹⁷⁷ Although a multiplicity of other risk factors, such as tobacco smoking, high intakes of saturated fats and cholesterol, lack of exercise, and obesity are common in this population, much attention has been focused on FH and its role as a risk factor in coronary heart disease. It now appears that there are two different FH mutations in the Afrikaans population, the commoner showing a 'high defective' LDL receptor number at the cell surface and the rarer showing a 'low defective' or 'negative' receptor phenotype.¹³⁴ At the DNA level two restriction enzyme site haplotypes have been shown to be associated with FH¹⁰⁸ and the actual molecular lesions have recently been defined.^{109 136}

Population screening for FH is now possible using specific oligonucleotide probes, but non-genetic risk factors must not be ignored and various organisations, in particular the National Heart Foundation, are increasing their educational efforts in this direction. A large scale Medical Research Council study (the CORIS project) carried out in the Western Cape Province identified the common risk factors, including FH, in many thousands of persons.¹⁷⁸ Opportunistic screening for FH using blood cholesterol levels has been carried out under the auspices of Genetic Services over the past six or seven years but, when considering the advisability of screening programmes, certain well defined criteria need to be satisfied before systematic screening should be instituted.¹⁷⁹ If cholesterol levels alone are used, case identification is difficult because of the hypercholesterolaemia owing to polygenic inheritance and dietary factors. Assuming the cholesterol levels could be reduced, the benefit in terms of reduced mortality and morbidity will have to be compared with the costs of screening and treatment, increased anxiety, and adverse effects of treatment. In order to identify those with FH it might be more economical to test those with a family history of coronary heart disease occurring at a young age. A recent study claims that FH may be as common in the

Ashkenazi Jews of Johannesburg as in the Afrikaans population.⁶³

Variegate porphyria (VP)

The pioneering genealogical research into variegate porphyria (VP) among Afrikaans speaking people in South Africa was carried out more than 25 years ago.¹⁸ Nevertheless, it would appear that we still do not know the actual number of South Africans with the gene. It is claimed that there are fewer than 1500 documented cases from among what is estimated to be 10 000 to 20 000 persons with the gene.¹⁸⁰ The situation is complicated by the fact that acute intermittent porphyria (AIP) may also be relatively common in the Afrikaans population; AIP may be even more common among the 'Coloured' or mixed race people than among the whites.¹⁸⁰ The epidemiology of these different forms of porphyria needs to be investigated if a rational discussion on screening programmes is to be initiated. The locus for VP has recently been assigned by classical linkage studies to chromosome 14q.¹⁸¹

Haemolytic disease of the newborn

The State has provided a free ABO, Rhesus, and antibodies testing service for all pregnant women since 1956 and the number of tests carried out is now about 600 000 per year, including about 86 000 tests on newborns (Genetic Services Report 1985/1986). Between 1959 and 1968, there were approximately 40 infant deaths per 100 000 live births (whites, 'Coloured', and Indians) owing to haemolytic disease of the newborn, but the figure was reduced to 2 or 3 per 100 000 births by 1980/82. Data for blacks are not available but the rate of rhesus (D) negatives is about one fifth lower than in whites; one in thirty marriages is 'at risk' for a rhesus incompatible baby. Anti-Rh(D) prophylaxis was introduced in 1968 and the number of doses used has increased steadily ever since, so that by 1986 over 14 000 doses were distributed throughout the country.¹⁸² It has been calculated that whereas the crude utilisation rate for blacks has been 14%, 18%, and 20% in the years 1983, 1984, and 1985, respectively, the corresponding figures were 94%, 93%, and 89% for whites; 63%, 59%, and 65% for Indians; and 49%, 45%, and 51% for 'Coloureds'.¹⁸² The overall utilisation rates for the three years were 41%, 42%, and 44% and, when compared with the utilisation rate of 30% for 1973 (the only earlier year for which a figure was available), would indicate an improvement over the 12 year period. There is obviously a great need, however, to improve the service for the populations other than whites, in particular for the blacks. Until this has happened there will be no real incentive to explore the possibility of giving anti-D immunoglobulin antenatally

or of using genetically engineered anti-D. Continued education of the public, as well as doctors in training, is essential if this prophylaxis programme is to be successful. Better access to improved health care services, particularly in the rural areas, will be needed before a significant impact is made on the problem as it affects the black population.

PRENATAL DIAGNOSIS

Amniocentesis was introduced to South Africa in 1969 by workers in Johannesburg.¹⁸³ The numbers increased slowly over the following years, both in Johannesburg and Cape Town, and the practice was extended to other centres in due course. At the South African Institute for Medical Research, Johannesburg, the numbers 'took off' in 1974 when 70 samples were processed; within two years the number had doubled.¹⁸³ A review of the Johannesburg experience for the period January 1976 to December 1977 reported that amniotic fluid had been collected from 438 patients, 55% at the Academic Hospital Clinic and 45% in the rooms of private practitioners.¹⁸⁴ Fewer than 2% of the patients were, however, drawn from the black or 'Coloured' communities. Abnormalities were detected in 4.9% of fetuses and the spontaneous abortion rate was 3%. Advanced maternal age (AMA) was the commonest indication (61%), followed by previous neural tube defects (NTDs) (18%), and previous Down's syndrome (11%). The experience of the Department of Human Genetics, University of Cape Town, for the five year period 1973 to 1977 was somewhat similar, although the number of cases was smaller: 434 amniocenteses with 54% for AMA, 12% for previous NTDs, and 14% for a previous child with Down's syndrome; the fetal loss rate was 3%.¹⁸⁵

The largest South African series of amniocenteses has recently been reported by Johannesburg workers,¹⁸⁶ namely 4554 cases during the decade 1976 to 1985. This shows a fivefold increase in the demand over the 10 years. AMA constituted the indication in 73.5% of the cases, 8.8% for previous NTDs, 7% for previous Down's syndrome. A correct prenatal diagnosis was made in 99.9% of cases and abnormalities were detected in 3.2% of pregnancies. The spontaneous abortion rate was only 0.7%. Seven South African laboratories participated in a two year collaborative study to analyse the cytogenetic studies carried out on nearly 10 000 cases: 2200 of the tests were to establish prenatal chromosome status and 3.7% showed a chromosome abnormality in the fetus.¹⁸⁷

The relatively restrictive abortion law (Abortion and Sterilization Act 1975) had the effect of inhibiting the development of fetal blood sampling in the 1970s and, more recently, chorionic villus sampling (CVS) as well. Obstetrician and gynaecologist colleagues

were not in a position to practise and acquire these skills because the number of patients undergoing legal midtrimester terminations has remained small. Although more than 45 000 CVS experiences had been recorded world wide up to March 1988,¹⁸⁸ the only report of CVS being carried out in South Africa is a single series of 60 cases reported from Johannesburg.¹⁷⁶ The miscarriage rate was 4%, slightly higher than the mean rate for the large series referred to above, but not significantly so because of the small numbers involved.

According to statistics published by the Department of National Health and Population Development (Genetic Services Reports 1985 and 1986), chromosome investigations were carried out on 15 668 amniotic fluid samples between 1977 and 1986, about a third of the number being carried out in Johannesburg. In Johannesburg, prenatal diagnostic services are used mainly by whites and it is estimated that about 35% of white women at risk (that is, aged 35 years or over) now take advantage of the test.¹⁸⁶ At the very busy Baragwanath Hospital in Soweto, black women often present too late in pregnancy for prenatal testing to be offered. It has been estimated that if black women presented for the test in the same proportion as whites the demand for the service would increase tenfold (the numbers are five times greater and the pregnancy rate approximately twice as high). It must also be pointed out, however, that some members of the black community are reluctant to terminate a pregnancy for Down's syndrome, or for any genetic abnormality for that matter. The well informed, and this includes those who have already given birth to a child with Down's syndrome and have presented for counselling, show very similar attitudes to abortion to most white patients (Kromberg and Kaplan, personal communication). The attitudes of black parents to the birth of a child with albinism have been researched and are also very similar to those of white parents.¹⁸⁹

Human Genetics Training

A questionnaire type survey on human genetics training was carried out in 1986 among the seven medical schools in South Africa (Op't Hof, personal communication). One school reported that "no specific course in human genetics is provided . . . students receive instruction in genetic counselling during their obstetrics time and (in) the basic first and third years". At five medical schools the subject is taught for an average of 35 hours (range 20 to 48 hours) during the course, but at one university only two hours were allocated for the purpose. Five schools were of the opinion that their qualifying doctors were not adequately equipped to provide genetic counselling, but all six felt that their graduates would know how to refer patients for such counselling. The view

of five schools was that genetic counsellors should be fully licensed physicians but four held that specialist medical scientists with a PhD degree, adequate experience in a medical environment, registration with the South African Medical and Dental Council, and with 'medical cover' should be allowed to provide counselling.

BSc(Honours) degrees in human genetics are offered at three of the medical schools and some of these graduates, as well as other science graduates, proceed to higher degrees (MSc or PhD) in medical genetics topics. One university department of human genetics has students taking an MSc degree by course work and short research report in which there is a strong emphasis on genetic counselling.

The DNHPD has, over the years, offered courses for the training of genetics nurses and has called on academics to assist.

The future

It may be expected that as full departments of human/medical genetics are established in all South African medical schools, greater clarity will emerge on the requirements for training doctors competent in the diagnosis and management of inherited disorders. At this stage, most people involved in medical education (under- and postgraduate) would agree that there is a need for more human genetics to be included in the medical curriculum.

There are five medically qualified clinical geneticists in South Africa who practice full time but these, like other medical consultants, are unevenly distributed; three are to be found in one medical school, namely that of the University of Cape Town, and here there are also four part timers who have been involved in the discipline for many years. In addition there are four clinicians with a strong interest in medical genetics but who have received no formal training. According to the recommendations of the United Kingdom Clinical Genetics Society Working Party on regional genetic services,¹⁹⁰ the specialty of clinical genetics would need a minimum of two consultants for a population of 1½ to 3 million if it were to develop and fulfil the perceived need. For its population of over 30 million South Africa would need between 20 and 40 consultants. It is apparent, therefore, that there is a gross shortage of trained clinical/medical geneticists as well as a shortage of training posts. In the teaching hospitals, doctors at registrar level in the recognised disciplines are too overworked to be able to devote time to gaining experience in medical genetics. In addition, it must be pointed out that there is a serious shortage of clinical laboratory geneticists in most centres and, although the Department of National Health and Population Development (Genetic Services) 'encourages' the laboratory investigation of genetic disorders by

making a financial contribution to the cost of the tests, the setting up and staffing of the laboratories is left to the already overextended university departments.

If genetic services are to expand to meet the needs of the population, a great deal of careful planning will be necessary. There are still probably too few clinical geneticists to constitute 'a critical mass' and, until recently, the Genetic Services Division of the DNHPD has not specifically included the clinical geneticists in the planning of services. This is probably a bad time to call for an expansion of genetic services: academic medicine and overall health care are on the decline owing to inadequate resources, fragmentation of health care services, failure to recognise the importance of academic medicine, and continuing discrimination in the provision of medical care.¹⁹¹ The State is proceeding with the privatisation of health services and one of the motives for this must be the poor and deteriorating economic state of the country, occasioned by the economic sanctions imposed by foreign countries, as well as by the apartheid system itself, which is wasteful of human and other resources.

The Vice-Chancellor of the University of the Witwatersrand has recently drawn attention to the serious 'brain drain' which the country is experiencing, pointing out that 44 of the 128 non-clinical academics (out of a total of 948 full time and 91 major time staff) who resigned from the university staff in 1988 have left the country.¹⁹² It is feared that the proportion of clinical staff who resigned and left the country is even higher. "The cost of travelling abroad to conferences and sporadic academic boycotting accentuate the isolation . . . General anxiety about the future, and for the young white man the prospect of military service are the main reasons for leaving."¹⁹²

The Southern African Society of Human Genetics was founded in 1986 with the express aims of advancing the discipline by facilitating contact between human geneticists, as well as between human geneticists and workers in related fields. Many of us have enjoyed the help and encouragement of fellow scientists in other countries and some of our own contributions have been facilitated to a considerable extent by international collaboration. The Society has held three Congresses and some overseas scientists have accepted invitations to participate in them. Others have declined and have informed us that this is because of the political situation in the country. Some foreign scientists have refused to share computer software and international journals have declined to publish articles by South African scientists because the writers live and work in South Africa. The problem surrounding the World Archaeological Congress that was to have taken place in Southampton in 1986 is well known.¹⁹³⁻¹⁹⁵ We cannot deny or wish away the academic boycott and there is the very real threat that it may get worse. Some South African

colleagues believe that there is *nothing* we can do about it, that it has got out of control, and represents an emotional response by some sectors of the international community. Others feel challenged to reassess their values as scientists and as citizens, acknowledging that science cannot flourish in a repressive society; scientists need to be free to think their thoughts and formulate answers to the questions posed by nature. Concerned South African scientists need to engage in discussion about ways in which the public (and politicians) can be better informed about the ways in which research can help improve the quality of life of the various communities, black and white.

No reputable human geneticists seriously believe that there are superior and inferior races and no South African scientists have lent their support (as scientists) to the Government's apartheid policy. None has participated, at the Government's request, in the exercise of race classification and some have spoken out against the practice.¹⁹⁶⁻¹⁹⁸ When the Government decreed 30 years ago that the race of the donor of blood for transfusion should be indicated on the container, South African academics marched in protest. Blood group gene frequency data on the various populations were presented and analysed to show that there was no good serogenetic reason for the practice.¹⁹⁹

Individual members of the medical profession, including medical geneticists, need to be continuously diligent in rooting out racial discrimination from the practice of their profession and must confront institutionalised racism wherever it occurs.²⁰⁰ The organised medical profession must be encouraged to speak out in favour of the just allocation of scarce medical resources.²⁰¹⁻²⁰⁸ The National Medical and Dental Association, representing only 5% of the profession, has done so since it was founded in 1983 and the Medical Association of South Africa, with perhaps 70% of doctors as members, has recently also taken a stronger public stand on these issues.²⁰⁹ Inequities must be removed and equal access to health care, including genetic services, ensured.

At the Second Congress of the Southern African Society of Human Genetics held in Cape Town in September 1988, it was unanimously agreed that the Society should inform fellow scientists, within and without South Africa, that the policy of the Society, since its inception in 1986, is summed up in the three sentences which appear on its official note paper and which are included in the Constitution of the Society, to which all members subscribe:

"This Society is formally committed to the maintenance of ethical and professional standards in all its affairs and activities. It is opposed to any discrimination on the grounds of race, religion or sex, believing such discrimination to be incompatible with the ethical practice of medicine and research.

The Society is committed to the promotion of science in a nondiscriminatory, just and peaceful society."

Will medical genetics have any role to play in the envisaged democratic, non-racial, post-apartheid society? With greater emphasis on primary health care and preventive medicine, the IMRs among the present underprivileged populations, including those in the rural areas, will drop and the demand for genetic services will increase. These services will be developed only if our medical schools provide improved and expanded under- and postgraduate training in medical genetics. And this training will be possible only if there is a strong community of academics vigorously pursuing high quality basic and applied research. Science is an international activity and an effective academic boycott will result in impoverishment and decline from which it will take a long time to recover.

There are no private medical schools or academic hospitals in South Africa; all are dependent on the State for their funding. One of the leading teaching hospitals has received no increase in funding in real terms over the last 10 years²⁰⁸ and this must be true for all the teaching hospitals. The government's policy of privatisation of health care, coupled with its adherence to the tricameral constitution (a variation on the apartheid theme), which results in the wasteful fragmentation of health services, means that the medical schools are being placed under extreme pressure to cut back on expenditure and, according to Professor S R Benatar, Head of the Department of Medicine at the University of Cape Town/Groote Schuur Hospital, may result in the teaching hospitals becoming "large centres for the treatment of the old, the infirm, and the indigent by relatively junior medical staff who have little time or inclination for academic activities and who have to use predominantly old and outdated equipment".²⁰⁸

This legitimate fear for the future of academic medicine is shared by many South African academics and does not augur well for the immediate future of medical genetics, still a relatively young discipline, in the country. Genetic services cannot be viewed except in the context of health care in general. Although South Africa spends 5-7% of its GNP on health, there is a strikingly disproportionate expenditure on Africans (3% to 3.5% of the GNP) compared with whites (13% to 14% of the GNP).²¹⁰ Deaths from diseases associated with poor socioeconomic conditions have declined during the 1980s but the differentials on the basis of race are still unacceptably great.²¹¹ The Administrator of the Transvaal (probably the most conservative and reactionary of the country's four provinces) has stated that South Africa can no longer afford apartheid in health services.²¹² The political climate in South Africa would seem to be changing for the better and it is to be hoped that this will be

conducive to the transformation of a racially segregated, unjust social order into one characterised by peace and justice. Only then will an equitable health care delivery system be possible, with medical genetics playing an important role.

I am grateful to a number of friends and colleagues for reading and critically evaluating an earlier draft of this paper, as well as for the invaluable information they provided. Some do not agree with my interpretations or the way in which I have presented the facts. Some have strenuously objected to my assessment of the medical genetics scene. It goes without saying that I alone am responsible for what I have written. I do hope, however, that this review will stimulate discussion about ways in which genetic services in South Africa may be improved. There may well be lessons to be learned by medical geneticists in other countries where access to the services by the 'haves' and the 'have nots' is as disparate as it is in South Africa.

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