George Fraser

Personal Details	
Name	George Fraser
Dates	1932
Place of Birth	Uzhhorod (Ukraine)
Main work places	London, Leiden, Adelaide, Seattle, Oxford
Principal field of work	Human genetics
Short biography	To follow

Interview	
Recorded interview made	Yes
Interviewer	Peter Harper
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This document is based on a conversation between George Fraser and Peter Harper on 3 February 2005 at the Galton Laboratory, London.

PSH. George, can I start at the beginning and ask where were you born and brought up?

GF. I was born in Užhorod— I must tell you a little story about Užhorod. An elderly gentleman died and went to heaven where he was received by Saint Peter.

'Where were you born?' asked Saint Peter.

'The Austro-Hungarian Empire' was the reply.

'Where did you go to school?'

'Czechoslovakia.'

'Where did you get married?'

'Carpatho-Ruthenia. I was married on 15 March 1939 when Carpatho-Ruthenia was an independent republic for one day.'

'Where did you have children?

'Hungary.'

'Where did your children grow up?'

'The Union of Soviet Socialist Republics.'

'Where did you die?'

'Ukraine.'

Saint Peter reflected on this unusual set of answers.

'Perhaps you have been sent to the wrong place because we do not have facilities for tourism up here. Why did you move around so much down there?'

'Move around? I was born in Užhorod and I died in Užhorod and I never once left Užhorod during my entire life'

PSH. Am I right it was 1932 when you were born?

GF. Yes, on 3 March.

PSH. And what year was it you came to England?

GF. 1939.

PHS. So that was pretty soon before the war.

GF. Yes, I shall tell you the circumstances. My father was a chess player all his life. At that time, we lived in Bratislava, the capital of Slovakia. Early in 1939, at the time when Czechoslovakia was dissolving under German pressure, my father was invited to play in a chess tournament in England. On 14 March 1939, Slovakia became independent and later in March my father left for England. My mother told him when he telephoned "You had better not come back"; the Fascist Hlinka Guard were looking for him because of his left-wing politics. He obtained permission for my mother and for me to join him and we arrived in England on 27 April 1939.

It was a very stressful time. The trains from Bratislava westwards through Prague, recently occupied by the Germans, were scarce and overcrowded. My mother managed to fight her way on to a train but she was jostled so much in the process that she had to let go of my hand and I was left weeping bitterly on the platform. Eventually, I was pulled in through the window—a trauma which I have remembered throughout my life.

PSH. I can imagine that. So then you went to school in England.

GF. Yes. After the Second World War started in September 1939, I was evacuated from London where my parents were living as refugees. I went to a children's home and orphanage in Cheshire and attended a local primary school. The headmaster wrote to my parents that their son should be in a school which could cater more adequately for his talents. Some time later, my parents moved from London to Oxford where my father was to study in order to convert his medical degree from the German Charles University in Prague to an English qualification. When my parents reached Oxford, my mother went to see the Reverend Wilfrid Oldaker, the headmaster of Christ Church Cathedral School, taking the letter from the school in Cheshire with her. The kind Reverend Wilfrid Oldaker told my mother that he would give me a chance. He said that I could sing in the Cathedral Choir and obtain a free education, but my mother told him that I had no talent for singing. "Never mind," said the kind Reverend Wilfrid Oldaker, "we will take him anyway. We have a

place for him as a day boy, and you will pay whatever you can whenever you can." I have never encountered such magnanimity since.

Subsequently, the Reverend Wilfrid Oldaker wanted to put me in for a scholarship to Eton but foreign-born boys were not accepted for the scholarship examination, So, I won a scholarship to Winchester College. After Winchester, I went to Paris for a year, then to Trinity College, Cambridge, in 1950.

PSH. Can I ask was there any scientific or medical background in your family?

GF. My father was a general practitioner all his working life; he greatly enjoyed his contacts with his patients. One of his brothers was a brilliant mathematician.

PSH. In your essay on Lionel Penrose, you mentioned that your father was actually national chess champion.

GF. Yes, that's right. My father competed many times for the British Chess Championship; he won once in 1957 at the age of 59 years. Jonathan Penrose won very often, ten times between 1958 and 1969. My father is the oldest player who has been champion and Jonathan Penrose is the youngest.

PSH. Well, even winning the British Chess Championship just once represents a pretty good record.

GF. Yes. My father held the title of FIDE International Master.

PSH. Did your mother have any scientific or medical interests?

GF. My parents lived in Budapest during the First World War, and my father was an officer in the Austro-Hungarian army. He was wounded and spent a long time in hospital. After leaving the hospital towards the end of the war, both my mother and my father entered medical school.

In 1919, my parents moved to the neighbouring, newly created, republic of Czechoslovakia where my mother had been born. My father was able to complete his studies of medicine at the German Charles University in Prague, but my mother could not resume her studies since she had to work to keep the family finances afloat. However, after my father qualified in medicine, she always assisted him substantially in running his general practice; that was her main occupation.

The Czechoslovak authorities did not allow my father, as a foreigner, to practise in the large towns of the country, where, as a fanatical player of chess, he would have liked to live. Instead, he was sent to the remote easternmost Czechoslovak province of Carpatho-Ruthenia, to the village of Kosino where the family of George Klein of Stockholm lived at the time. That is how I came to be born in a hospital in Užhorod, the capital of the province. Later, my father acquired Czechoslovak citizenship and we moved to Bratislava, the capital of Slovakia.

He actually practiced in the village of Kosino (Mezőkaszony in Hungarian) where the family of George Klein, now of Stockholm, lived at the time; my father would have attended his birth, being the only doctor for miles around, had George's mother not attended a hospital in Budapest for her confinement in 1925.

PSH. When you reached Cambridge, am I right that initially you got a scholarship to read mathematics? I am wondering what took you in the direction of more biological sciences.

GF. It was my father who influenced me to study medicine. I have never thought that this was a good choice. Although I won a scholarship to Trinity College in mathematics, I loved Ancient Greek and Latin and I did very well in classical studies during my first two years at Winchester College. I have always regretted that I had to give up classical studies at the tender age of fourteen years.

When, after those first two years, my father informed the relevant masters at Winchester College that I was to enter the specialised science ladder, they thought that this was a poor decision. So do I, but this does not detract from my love and respect for my father. He had had a hard life and he could not conceive how it might be possible to earn a living as a classicist. He thought that a medical degree represented a safe insurance with respect to making a living.

PSH. So, in Cambridge you eventually did your Part II of the Natural Sciences Tripos in Genetics with R A Fisher?

GF. Yes, I still had hankerings after mathematics. I had had more hankerings after classics, but that possibility had long passed. The training for Genetics was mathematical to a substantial extent. In Cambridge, it was possible to finish Part I of the Natural Sciences Tripos

in two years; you were then free to study anything you wanted during the third year of the degree course. I remember one of my friends who studied Persian during his third year even though he was destined for

medicine. I went to see Ronald Fisher at the end of my second year. “Well, yes” he said “we were given permission to teach a Part II course last year, when there were no applicants; this year you are the only one. I am happy to accept you; your required applied field can be serology with Robin Coombs.”

PSH. So were you really the only student during that year?

GF. Yes.

PSH. How did you find Fisher as a person to work with?

GF. I always had the greatest respect and liking for Fisher. I saw quite a lot of him as I was the only student attending four courses of lectures of which two were given by Fisher. There were usually two or three other people attending the lectures; their status was different. Fisher always treated me very courteously. I was really astonished later in life to learn that he had a reputation for being arrogant and difficult to approach; I certainly would not subscribe to this point of view.

PSH. At that time, had you already decided to try and build genetics into your career or were you still set on being a clinician?

GF. It seemed advisable to complete a degree in medicine in any event. The thought of Genetics as a career was definitely in my mind; I wanted to go to University College Hospital for my clinical years because I knew that Haldane and Penrose were there. I was not accepted, and I went to the London Hospital where I met Harry Harris. I kept in touch from a distance with Lionel Penrose, because he knew my father as a result of their common interest in chess. In addition, they collaborated in striving to preserve peace within the framework of the Medical Association for the Prevention of War. Richard Doll was also a leading light of the Medical Association for the Prevention of War.

PSH. I didn’t know that Harry Harris was at the London then. Am I right that Bette Robson was also there?

GF. Yes. I do not remember the exact dates they were both there, but I believe that these included my time as a clinical student (1953-1956).

PSH. I saw that your first paper is co-authored with them on a new inherited plasma protein.

GF. Yes. That was at the time when I was doing my PhD at the Galton Laboratory in 1957-9. I was travelling around the country to study

families with the Pendred syndrome of deafness with goitre. Harry Harris and Bette Robson wanted familial serum samples and I was taking blood for the Pendred syndrome studies. Those were the origins of the paper on the new inherited plasma protein (*Fraser G R, Harris H and Robson E B: A new genetically determined plasma protein in man.* ***Lancet 1****: 1023-1024, 1959).* It was a fortuitous finding, not associated with the Pendred syndrome.

PSH. You must have got quite a lot of clinical experience during your student years because the London Hospital was a pretty busy hospital at that time.

GF. Yes. I am amazed how well I remember the London Hospital and so many of the excellent consultants of more than half a century ago. I do not know if the London Hospital was exceptional in this respect among London teaching hospitals. In any event, I met some very fine clinicians of a quality which, in my opinion, is more rare today.

I also remember the harsh living conditions in the surrounding poor areas of Whitechapel when I attended home confinements as a clinical student in 1956-7.

PSH. Is it right that you won a prize in obstetrics?

GF. All the senior students wrote essays in competitions for several prizes. I won the George Riddoch Prize in Neurology and a prize in Clinical Obstetrics and Gynaecology.

PSH. Then you qualified in 1957, and you got an MRC Scholarship to come to work with Penrose. I am amazed how important those early MRC Scholarships have been in setting people on their career. How did you get an MRC Scholarship? Did you just ask Penrose about applying?

GF. The relevant MRC authorities were enthusiastic in encouraging individuals to apply for these scholarships; there were absolutely no problems in obtaining one in human/medical genetics for three years with Lionel Penrose. In the event, I held the scholarship for only two years from October 1957. When I told Lionel that I would not be staying for the third year of the scholarship, having accepted a job in Oxford with Alan Stevenson in the MRC Population Genetics Research Unit in Oxford, Lionel said: “I am sorry. It’s a pity you didn’t do your PhD”. I said, “Professor, I have written my PhD thesis.” He said “Really? What is it about?” I told him that it was entitled *Deafness with Goitre (Syndrome of Pendred) and some related aspects of Thyroid Disease.* I gave the

completed thesis to him before I left the Galton Laboratory in September 1959.

PSH. I'm intrigued by the PhD and that study, because, am I right, that when you had an MRC studentship or scholarship you didn't actually have to have a particular project?

GF. Well there wasn't very much teaching at the Galton Laboratory. I don't know what would have happened had I taken my scholarship to Ronald Fisher who offered me a place as a postgraduate student in Cambridge. At the Galton Laboratory, Cedric Smith gave a few lectures as did Lionel Penrose. I saw J B S Haldane a few times when I attended his Drosophila classes. That's all the teaching I remember. The main object of these scholarships was to write a thesis and obtain a PhD degree.

PSH. So how did it happen that you decided to take on deafness and specifically deafness with goitre? How did that come about?

GF. It was a matter of a very simple decision. I told Harry Harris that I did not have a subject for my thesis; this was already several months into the scholarship. Harry Harris told me that I should go to see Dr Bob Trotter at University College Hospital, who had been discussing some ideas with him. I went to see Bob, and in three minutes a decision was taken. Together with Dr Margaret Morgans, Bob was about to publish a paper *(Morgans, M E and Trotter, W R: Association of congenital deafness with goitre: the nature of the thyroid defect.* ***Lancet 2:*** *607-609, 1958).* They had described two sibs with this association of congenital deafness with goitre, they had defined the nature of the thyroid defect, and they had found several reports in the literature of this association in sibs. They concluded: *We report these cases as examples of a syndrome, of both genetic and biochemical interest, which might well repay further study if more cases come to light.*

The die was cast; I embarked on bringing more cases to light for further study.

PSH. And Dr Trotter was a physician, a thyroid physician? Not especially involved with the hearing side?

GF. He was an eminent thyroid physician; he was not particularly interested in deafness.

I should like to relate an episode which occurred during our collaboration because it illustrates the pitfalls of scientific research. Dr Trotter had a

laboratory colleague who had set up a preparation of slices of thyroid glands from sheep, through which he could circulate fluids and test whether they contained any substance which blocked the immediate binding of inorganic iodide, trapped by the thyroid gland from the circulating blood, to thyroglobulin, this being the first stage in thyroid hormone synthesis; this was the stage which had been found to be defective in patients with the Pendred syndrome. Dr Trotter sent sera from our patients with the Pendred syndrome to this colleague, together with appropriate control sera from members of their families. There was great elation in our little group when it was shown that the sera from the patients caused marked blocking binding of inorganic iodide, whereas the control sera did not. We thought that we were on the track of an inborn error of metabolism, which was leading to the production of an abnormal metabolite circulating in the serum and causing the blocking of binding of inorganic iodide to thyroglobulin.

For the next instalment of this salutary lesson on the frail nature of scientific research, we must go back thirty years to the studies of Russell Brain in the East End of London in 1927 (*Brain, W R: Heredity in simple goitre.* ***Quarterly Journal of Medicine 20:*** *303-319, 1927).* In his paper, Brain reported no less than five families containing twelve persons affected with the Pendred syndrome. Despite the destruction of large parts of the East End of London by bombing during the intervening Second World War, I was able, with the help of Sir Russell Brain, to trace three of these five families, thirty years after he had seen them. In the course of a visit to the East End of London, I collected blood samples from a number of members, both affected and unaffected, of these three families. The samples were duly sent for testing by the sheep thyroid slices. Consternation ensued! None of the specimens caused any blocking of binding of inorganic iodide to thyroglobulin. Dr Trotter was inclined to believe, since he had not seen the patients himself, that I had made diagnostic errors in believing that these individuals in the East End of London were affected with the Pendred syndrome. I was, of course, despondent initially, but I shall never forget the moment of epiphany a few days later when I realized what had happened.

Previously, the sera of patients had been sent for testing by the sheep thyroid slices from Dr Trotter's clinic where the patients had been tested for the blocking of binding of inorganic iodide to thyroglobulin, which was pathognomonic for the Pendred syndrome. Methimazole and perchlorate were given to the patient by mouth as part of this testing, and it was the methimazole which was giving rise to the marked blocking of binding of inorganic iodide to thyroglobulin in the sheep thyroid slices. My patients from the East End of London, on the other hand, had not

passed through Dr Trotter's clinic; obviously there was no methimazole in their sera at the time of the test using the sheep thyroid slices.

Sic transit gloria mundi!

PSH. I notice there are quite a few early papers of yours, apart from the ones on deafness and goitre, which are broader in the thyroid field. Would that have been because of his influence?

GF. No. I did not do anything of that sort during my tenure of the MRC Scholarship. I did that work during my time in Oxford afterwards.

PSH. Right.

GF. When I was working in Oxford, I met Professor D V Hubble, a paediatrician from Birmingham. With his help, I saw 28 children in Birmingham and Oxford with a presumptive diagnosis of athyreotic cretinism. I tested them for the PTC (phenylthiocarbamide)-tasting polymorphism and found an excess of non-tasters, which had been reported before. I have no idea what this finding *(Fraser, G R: Cretinism and taste sensitivity to phenylthiocarbamide.* ***Lancet 1:*** *964-965, 1961)* may signify. And then I carried out a genetical study of goitre in the Oxford area, involving mainly 57 unselected male adults who had undergone thyroidectomy *(Fraser, G R: A genetical study of goitre.* ***Annals of Human Genetics 26:*** *335-346, 1963).* I chose to study males because of their reduced predisposition to thyroid disease as compared to females. A notable finding was that of one case of XXY Klinefelter syndrome among twelve infertile males with non-toxic goitre. Other such cases have been reported, and it is tempting to postulate that XXY males may be predisposed to a disease which is more characteristically found among females.

PSH. Can I just go back now to the Pendred syndrome, because you were the person that put the condition on the map as a genetic disorder. Was it actually known as the Pendred syndrome before or did you christen it?

GF. I collaborated with Dr Morgans and Dr Trotter in putting the syndrome on the map and in studying the literature. Let us say that all three of us were present at the christening of the syndrome when we found the relevant article by Vaughan Pendred *(Deaf-mutism and goitre.* ***Lancet 2:*** *532,* 1896). Even though the article consisted of just one paragraph, it gave such a good description of the condition which we were studying that it seemed self-evident that we should call it the Pendred syndrome. Thus, the first sentence of our joint paper in 1960 was: *Pendred (1896) gave a brief account of two sibs with goitre and*

deaf-mutism, living in an area where goitre was not endemic. The first sentence of my 1965 paper was very similar.

Fraser, G R, Morgans, M E, and Trotter, W R: The syndrome of sporadic goitre and congenital deafness. ***Quarterly Journal of Medicine 29:*** *279-295, 1960.*

Fraser, G R: Association of congenital deafness with goitre (syndrome of Pendred: a study of 207 families. ***Annals of Human Genetics 28:*** *201-249, 1965.*

PSH. At what point then did you broaden your study of deafness because I am quite struck that in some of your early papers, other deafness syndromes play a prominent part, like the Fraser syndrome, the cardiac syndrome of Jervell and Lange-Nielsen, and the Usher syndrome; none of those would have been found in studies of thyroid disease.

GF. I had finished my study of the Pendred syndrome in connection with writing my PhD thesis. The MRC Population Genetics Research Unit in Oxford was not a place where specific assignments were allocated to the research staff. They were supposed to accumulate research in population genetics; no one told them how to do it. The only approach to a plan for research which I presented was: *I want to study profound childhood deafness.*

I had an idea that the syndrome of Jervell and Lange-Nielsen *(Jervell, A and Lange-Nielsen, F: Congenital deaf-mutism, functional heart disease with prolongation of QT interval and sudden death.* ***American Heart Journal 54:*** *59-68, 1957)* might not be as rare as it seemed, and that if I were to study very large numbers of deaf individuals, I might obtain information about its frequency. While I was in Oxford, I studied 2330 children in special schools for the deaf in the United Kingdom and Ireland. I went to a number of residential schools containing 100-300 children each, and also to some smaller schools. I spent three or four days at each of the larger schools; during that time, I examined all the children and obtained an electrocardiogram tracing from each of them. In Ireland (Belfast and Dublin), I was accompanied by my long-term collaborator in these studies, Peter Froggatt.

PSH. You took the electrocardiograph machine with you?

GF. Yes, one of the specific aims of this study, and of visiting these schools, was to take an electrocardiogram of each child in order to define the incidence of the syndrome of Jervell and Lange-Nielsen among them. In connection with the portable electrocardiograph, Stevenson did not

wish to buy the machine which cost £235 in those days. At the back of the Churchill Hospital in Oxford, there was a building called the MRC Electronic Workshop, or some similar name. Stevenson had the idea of asking this workshop to make an electrocardiograph. After several months, the machine duly turned up. I went to the first school for the deaf with this machine; it functioned only sporadically and, when it did function, the ECG tracings were of very poor quality, entirely unusable for the purpose of detecting the lengthening of the QT interval which is pathognomonic for the diagnosis of the syndrome of Jervell and Lange-Nielsen. So, I went to a firm in London which dealt in portable electrocardiographs, and I told them that I wanted to test out a machine during my field studies of deafness; they were understanding and provided me with a portable electrocardiograph on indefinite loan. Eventually, Stevenson bought it for £235.

PSH. Did you base your deafness study at all on Penrose's Colchester survey of mental defect? Because it was a very systematic study of deafness, and I just wonder whether you gained a parallel from your time at the Galton.

GF Yes, of course. I have always specifically emphasised this connection.
Penrose, L S: A clinical and genetic study of 1280 cases of mental defect (The 'Colchester Survey'). Medical Research Council Special Report 229, 1938.

Fraser, G R and Friedmann, A I: The Causes of Blindness in Childhood. A Study of 776 Children with Severe Visual Handicaps (with preface by L S Penrose). pp 245: Johns Hopkins Press, Baltimore, 1967.

Fraser, G R: The Causes of Profound Deafness in Childhood. A Study of 3,535 Individuals with Severe Hearing Loss Present at Birth or of Childhood Onset (with foreword by V A McKusick). pp 410: Johns Hopkins University Press, Baltimore and London, 1976

PSH. Yes.

GF. Such complete ascertainment of a disease or disability represents a simple approach, but I think that it has been very productive for a long time. In the case of deafness, it goes back to the nineteenth century. It continues to be productive today, even though individuals with such diseases or disabilities are not now segregated to such an extent.

PSH. That's very true. So you were at the Oxford unit for a couple of years?

GF. In my time, there was little permanence with respect to the research staffing of the MRC Population Genetics Research Unit. This was not because the staff were being asked to leave, but because it was a very difficult place in which to work. I remained for 25 months and John Edwards, Marco Fraccaro and Louis Woolf stayed for even shorter periods.

PSH. You must have been there soon after Stevenson had come from Northern Ireland.

GF. I was there from October 1959 to November 1961. I think that the unit had been founded a couple of years before that time. It was situated in a prefabricated building in a field in Headington, where there is now a vast university complex.

PSH. Stevenson, from what I gather, was not an easy person to work with.

GF. He was a very jovial person, but he had no great expertise in dealing with the ideas of his senior staff, at least during the couple of years which I spent in his unit.

PSH. I'm never quite clear why, in the first place, so many very good people went to work there and then, in the second place, why most of them didn't stay very long.

GF. In 1959, there were several talented individuals available, who had had training in the disciplines of human and medical genetics. They wanted an opportunity to work, and there were very few opportunities. These were new ideas, although the field expanded during my two years in Oxford, and more opportunities became available especially outside the United Kingdom. Because Stevenson had no great expertise in dealing with the ideas of his senior staff, John Edwards, Marco Fraccaro, Louis Woolf and I left the country. Jim Renwick accepted a job with Stevenson but joined Pontecorvo in Glasgow instead.

PSH. So am I right then, the next stage for you was with Motulsky in Seattle?

GF. Yes, as I said, after a couple of years, there were many more jobs available. While in Oxford, I wrote a long paper entitled: *Our genetical 'load'. A review of some aspects of genetical variation.* ***Annals of Human Genetics 25:*** *387-414, 1962.* This paper eventually led by a totally unexpected route to my name being attached as an eponym to the Fraser

syndrome; the main features of the condition were described as components of the 'syndrome of cryptophthalmos' in a short section of this long paper, dealing with genetical variation expressed in the form of multiple congenital malformations inherited in an autosomal recessive manner.

The ideas arising from my work in London and in Oxford, including those expressed in this paper, found some resonance at the Second International Congress of Human Genetics in Rome in 1961. I met several people there who expressed an interest in my future. I chose to join Motulsky

PSH. That again must have been fairly soon after Motulsky had set up the Seattle unit.

GF. Yes. I had met Motulsky previously during the time from 1957 to 1959 when I was doing my PhD at the Galton Laboratory. Many people came there for periods of varying lengths, including Motulsky who had been asked by the University of Washington in Seattle to prepare the creation of a Department of Medical Genetics.

PSH. Did you go to Seattle with any particular type of work in mind or did you see what was happening there and take it on from that point. I notice for instance that a lot of the Seattle publications of yours are population-based?

GF. I became involved with analysing the results of Motulsky's studies of frequencies of haemoglobinopathies and of G6PD deficiency in various populations. Most of my time in Seattle was spent with these studies, including several months of field work in Yugoslavia and Greece.

One aspect of this work led to a startling result a quarter of a century later. I worked in 1962 on calculating frequencies of alleles responsible for haemoglobinopathies, G6PD-deficiency, blood groups and serum groups in blood specimens collected by Motulsky in various countries including the Belgian Congo (now the Democratic Republic of Congo). Twenty-five years later, in 1987, Motulsky wrote me a letter stating that a stored serum specimen (L70) from his Leopoldville (Kinshasa) series, which was collected in 1959, had been found to be positive for HIV—one of the first cases to be recorded. And he asked me in his letter who this man, L70, was. Did I have the details of the subjects from whom he had collected blood in 1959?

I remember lists of numbers in the exercise books from which I had worked in Seattle. I do not remember that these books contained any

details (apart from gender) about the donors of the samples. And I had left the exercise books in Seattle 25 years previously! A journalist called Edward Hooper has made a career out of constructing polemical theories about the origins of HIV and AIDS. He came to see me in about 2000 and interrogated me at length about the exercise books. Hooper's views about specimen L70 are extensively discussed in his book *The River: a Journey back to the Sources of HIV and AIDS. Allen Lane: The Penguin Press, 1999.*

PSH. George, when you went to Seattle was this with the idea of a permanent post or was it a kind of further fellowship?

GF. It was a fellowship; I was not offered any permanent post when I left Oxford in November 1961. It was a difficult situation for me since I was an only child and my parents, who were living in London, did not enjoy good health. I was offered an opportunity to return to London, and to be near to my parents, in March 1963 when I replied to an advertisement placed in the British Medical Journal by Professor Arnold Sorsby who wanted to study blindness in childhood in the same way as I had studied profound childhood deafness.

PSH. I gather that the study was based at the Royal College of Surgeons?

GF. Yes. In the Department of Research in Ophthalmology.

PSH. Right. Because Sorsby had done a lot there already by then. Am I not right that around that time he was editing the Journal of Medical Genetics?

GF. Yes. Sorsby was largely instrumental in creating the journal and he was the first editor. He asked me to write some papers for the first issues. While I was working in his department, I wrote four papers in the two issues in the first volume in 1964 and two more in the first of the four issues in the second volume in 1965. Four of these six papers were derived from my studies of gene frequencies in Seattle, the data for them coming from Motulsky's expeditions to Taiwan and to the Philippines. I also wrote a review article on profound childhood deafness and an article with Sorsby on ocular refraction in twins. So, I fulfilled his request to help in providing material for the first issues.

PSH. To discuss your study of blindness then. Did you model that on your study of deafness as a kind of follow-on?

GF. I didn't have to think about the logistics or the techniques at all. It was a replica rather than a follow-on.

PSH. Am I right that both studies concentrated on special schools?

GF. Yes. I have already discussed this aspect of the deafness study. In the case of blindness, I visited schools containing 776 children. As a link between the two studies, I shall turn to cryptophthalmos, or the Fraser syndrome. In Oxford, I had been studying various groups of deaf children apart from those in special schools, and my index case with cryptophthalmos, Michele S, came to my attention in 1960, because Dr Brian Kirman, a friend of Penrose, was providing some care, at the Fountain Hospital in South London, for a small group of children who could not communicate at all. Michele, five years old at that time, was both deaf and blind.

In the blindness study which I did from Sorsby's department, I confined myself to schools for blind children; I was accompanied by an ophthalmologist, Alan Friedmann. During this study, I met Michele again.

PSH. So am I right that this Fraser syndrome patient came out of the deafness study rather than the blindness study?

GF. Yes, originally. She appears in my study on deafness as I have explained. During my subsequent study on blindness in Sorsby's department, I visited a school called Condover Hall near Shrewsbury, which catered for children who were both deaf and blind. Thus, I first met her in 1960, at the age of five, as part of the deafness study, and again in 1964, at the age of nine, as part of the blindness study. She appears as a proposita in both of my books which describe these two studies.

After I was told about Michele at the Fountain Hospital, I visited her home in rural Essex in March 1960. I spent an afternoon with her and with her parents. Michele behaved in a very wild way, almost like a wolf-child, reacting with a terrified scream to any attempted approach. I noticed that she seemed very fond of a large alarm clock which she pressed to her forehead for long periods. I suspected that there might be a conductive element to her deafness. As part of my studies of deafness in Oxford, I had been seeing groups of children with malformations of the outer and middle ears. I was collaborating in this study with an ENT surgeon, called Gavin Livingstone, who was trying to improve the hearing of these children by reconstructing the middle ear. Gavin Livingstone agreed to see Michele; he reconstructed the malformed ossicles of her middle ears, and Michele began to hear for the first time at the age of six years. By the time she was nine, she was keeping up with the other children at Condover Hall, a school for the deaf and blind, and

she was able to communicate. She has been well looked for many years in a home run by a charity called *Sense*, where I was able to meet her again at the age of 51 years.

Michele has lived a life which I believe to be a little more tolerable than it would have been without any hearing. Perhaps this small contribution to the improvement in the quality of the life of this girl represents a greater achievement than that of my name becoming attached to a syndrome, or even, in abbreviated form as *FRAS1*, to a gene.

PSH. So do you think she was mentally entirely normal?

GF. Probably. Nowadays, in reviews of the pleiotropic nature of this syndrome leading to widely variable degrees of manifestation in each of the organs which can be involved, it is accepted that the mental state can be normal, but this normality may, of course, be cloaked by sensory deprivation, especially when both eyes and, in addition, hearing are affected, as in Michele's case.

PSH. Yes. Just before we leave your time in London, Sorsby himself, what kind of a person was he to work with? Was he like the others who just let you get ahead and do things?

GF. Yes, he let me get ahead and do things as I thought best within the framework of the general remit to study the causes of blindness in children. I used this study to write an MD thesis for the University of Cambridge; It won the Raymond Horton-Smith Prize for the best MD thesis of the academical year 1965-6. Sorsby's ophthalmological colleague, Alan Friedmann, agreed to let me use the material which we had gathered, for my thesis in which his contribution was fully acknowledged. Moreover, he was the co-author of a book which was a verbatim reproduction of the thesis and which was published by the Johns Hopkins Press after being recommended by Victor McKusick. Lionel Penrose wrote a preface.

PSH. So your study was published as a book as well as an MD thesis presented to the University of Cambridge whereas your PhD had been presented to the University of London?

GF. Yes. To present it to the University of Cambridge seemed to me to be a good idea.

PSH. I think most MDs are with the University you originated from.

GF. Yes that is probably why. I remember later on when I put my papers in for a DSc degree, I could have chosen between Cambridge and London. Do you remember Professor John Thoday?

PSH. Yes.

GF. He saw my MD thesis in 1965 when he was asked to comment on it by the examiners. He told me a quarter of a century later, when I met him at the Fisher Centenary in Cambridge in 1990, that he had said that the quality of the thesis was such that it should have been presented for a DSc degree.

PSH. After your time in London, then, you went to Australia; how did that happen?

GF. My contract in the Department for Research in Ophthalmology was for three years. Towards the end of that period, I was called in to see the Secretary of the Royal College of Surgeons, to be told that my services would no longer be required after the appointed date for the end of the contract.

There was no possibility of getting any job in England after having stayed for such short periods in Oxford and in London, despite the fact that during these five years, I had collected material for two books and done much else besides. When I had been with Fisher as an undergraduate in 1952-3, he had had an Australian PhD student called Henry Bennett who had retained a fond memory of me. Actually, some time previously in 1960 or 1961, when I had been in Oxford, he had written to me and told me that he was very interested in Kuru and that he was contemplating the initiation of large-scale family studies in Papua New Guinea. He had wanted me to go to live in Okapi in Papua New Guinea for some time, in order to carry out such large-scale family studies. Jim Renwick told me that such an enterprise was bound to resolve the problem of the aetiology of Kuru because either I would catch the disease, proving that it is infectious, or the locals would eat me and get better, proving that it is a deficiency disease! I resisted the temptation to go to Papua New Guinea; fortunately, five years later, Henry Bennett told me that he now had a job for me in Adelaide rather than Okapi. Accordingly, I arrived in Adelaide on 1 January 1966.

PSH. Was this the same Bennett who started the Fisher archives?

GF. Yes, he has been devoted to Fisher ever since his time in Cambridge. After Fisher had been compelled to retire from his Chair in Cambridge in 1957 on grounds of age, he had several opportunities to continue his work

after his retirement; he accepted the excellent one which Henry Bennett and his colleagues offered him in Adelaide, where he died in 1962.

Henry worked on various books, archives and other projects involving Fisher after returning to Adelaide from Cambridge in the 1950s to become Professor of Genetics at a very young age. He may well still be continuing his work on Fisher.

PSH. What particular projects did you actually get going during the time you were in Adelaide?

GF. By that time the Kuru family studies had become redundant in that it had become clear that Henry Bennett's ideas about Kuru as a hereditary disease were not tenable. My appointment no longer had anything to do with the study of Kuru. Henry wanted to start a section of human genetics and he offered me a position as a Reader. I had to give lectures but I was not asked to do anything special in the way of research. I carried out extensive studies of blind children *(Fraser, G R: Causes of severe visual handicap among schoolchildren in South Australia. **Medical Journal of Australia 1:** 615-620, 1968),* and of persons with profound childhood deafness, both adults and children, in Adelaide and its surroundings. The studies on deafness are included in my book on profound childhood deafness published by the Johns Hopkins University Press much later in 1976.

It is in Adelaide that I met Oliver Mayo with whom I have remained in contact for 45 years. Forty-one years after we met, the book *Fifty Years of Human Genetics: a Festschrift and Liber Amicorum to celebrate the Life and Work of George Robert Fraser (editors Mayo O and Leach C), Wakefield Press, Kent Town, South Australia, 2007* was published on the occasion of my 75th birthday. Oliver had initiated this project in 2003 and I am most grateful to him and to his colleague, Carolyn Leach, for the very considerable time and effort which they devoted to editing the book. I served as their assistant; it was a most enjoyable experience. I should also like to express my gratitude to the 64 colleagues who accepted an invitation to contribute, and to their co-authors.

The book included two articles which I wrote.

Medical knowledge in the service of informed parental reproductive decision and choice: absence of implications for eugenic ideology, pp 287-298

Human genetics today: hopes and risks, pp 299-309

Oliver wrote an introduction, *The origin and purpose of this book, pp ix-xi,* and Carolyn wrote a Coda, *The completion of the book, page 468.*

Oliver's contribution *(Environment and complex disease, pp 427-430)* started with a theme taken from a chapter *(Disease and human genetics, pp 442-492)* which I wrote in a textbook of human genetics which we edited together and to which we wrote an introduction together *(pp 1-2).*
Fraser, G R and Mayo, O, eds: Textbook of Human Genetics. pp 524: Blackwell Scientific Publications, Oxford, 1975.

To go back, after this digression, to Adelaide in 1966, Oliver put several papers, some written in collaboration with me, together as chapters to make up his PhD thesis; I was his supervisor during the time when I was in Adelaide. One of our joint papers from this period contained a finding of some importance, confirmed by several later studies, that individuals of blood group A have higher serum-cholesterol levels than those of blood group O *(Mayo, O, Fraser, G R, and Stamatoyannopoulos, G: Genetic influences on serum cholesterol in two Greek villages.* ***Human Heredity 19:*** *86-99, 1969).*

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PSH. Was your association the basis for your joint textbook of human genetics? The one you edited with Oliver Mayo.

GF. Only in the sense that our friendship led to my arranging a job for Oliver for a few months in 1971 when I became Professor of Anthropogenetica (Human Genetics) in Leiden. He needed a job at that time because he had left Australia and there was no opportunity for him to go back immediately following the end of his fellowship in Edinburgh. The job in Leiden actually came with a lifetime contract in the Dutch Civil Service, but he only stayed for a few months before he was invited to return to Australia in order to take up an appointment in Adelaide. A gentleman called Per Saugman, who was a director of Blackwells, came to see us in Leiden and asked us to edit a textbook of human genetics

PSH. But before you went to Leiden you had had another spell in Seattle.

GF. Yes. It had been very tough on my parents when I went to Adelaide in January 1966, and, in order to give Henry Bennett plenty of time to arrange a replacement, I had informed him during the summer of 1966 that I would only stay for two years. My father died in May 1967, and I could think about jobs elsewhere than in England. Both McKusick and Motulsky offered me good positions, and there were other offers.

Motulsky had accepted a mission to create a department of medical genetics at the Albert Einstein University in New York. He was going to collect a talented team, and the department was going to be of outstanding quality. I accepted his offer, having already resigned from my job in

Adelaide some time previously. I was scheduled to go to Seattle in January 1968 and then on to New York at the end of 1968.

PSH. Yes

GF. I had a discussion with a removal firm, and I asked a representative to come with me to my university office to estimate the cost of transporting my books and papers to New York. When we reached the office, I said to the representative that before our discussion I had better read the telegram which had been placed on my desk. The telegram was from Motulsky; it said, in summary: "We are not going to New York."

Consternation reigned! I had refused the offer which McKusick had made after I had spent six weeks as a Visiting Professor at Johns Hopkins Hospital the previous year, explaining that I was accepting Motulsky's offer which had now vanished. I was due to leave Adelaide in four months.

I wrote a letter to Motulsky, explaining my situation, and he telephoned me as soon as he received the letter. He told me that when he had returned to Seattle from his last visit to New York, he had realised that he could not possibly leave all his friends and colleagues in Seattle.

I was naturally anxious about the turn which events had taken, and, with some trepidation, I asked Motulsky where this sudden epiphany, after years spent in organizing the department in New York, would leave me in four months' time when I was due to leave Adelaide. He answered that I had better come to Seattle for the year of 1968, as arranged, and we would then see what was to happen next.

PSH. So you then were back with the population genetics studies?

GF. Yes.

PSH. Can I ask, you did a lot of population studies on European populations, Yugoslavia and Greece and such like? Would they have started up then or was that later when you were based in Leiden?

GF. No, your chronology is wrong. The studies in Yugoslavia and Greece had been carried out during my previous time in Seattle as a fellow from 1961 to 1963. We were collaborating with Profesor Phaedon Fessas and his group in Athens. Motulsky and Fessas had arranged to study the frequencies of genes determining thalassaemias, abnormal haemoglobins, and G6PD deficiency in a complete ascertainment of the population of two villages in the Arta region of Greece. I was sent during

the summer of 1962 to conduct this study in collaboration with Greek colleagues in Athens *(Fraser, G R, Stamatoyannopoulos, G, Kattamis, C, Loukopoulos, D, Defaranas, B, Kitsos, C, Zannos-Mariolea, L, Choremis, C, Fessas, P, and Motulsky, A G: Thalassemias, abnormal hemoglobins and glucose-6-phosphate dehydrogenase deficiency in the Arta area of Greece: diagnostic and genetic aspects of complete village studies.* ***Annals of the New York Academy of Sciences 119:*** *415-435, 1964).* Several other papers came out of these studies including the one on serum-cholesterol levels and the ABO blood group which I have already mentioned *(Mayo, O, Fraser, G R, and Stamatoyannopoulos, G: Genetic influences on serum cholesterol in two Greek villages.* ***Human Heredity, 19:*** *86-99, 1969).*

I stayed in Arta for some months, and then I went on an extensive tour of Yugoslavia by car with a Yugoslav colleague, collecting blood specimens. I spent five months in all in Yugoslavia and Greece. You were referring to these five months in 1962, when you mentioned my European population studies. The studies in Greece were intended to have long-term consequences in that we gave information to each inhabitant of these two villages about their status with respect to haemoglobinopathies, and about the significance of this information with respect to their choice of marriage partner. Two similar projects were organized later in different areas of Greece within the framework of this collaboration between Athens and Seattle; these were carried out without my participation.

Subsequently, it was recognised that, in Greece at least, this form of genetical counselling within entire populations was not effective in that little or no notice was taken of the implications of the information and advice given. In 1992, thirty years after my participation in the Arta expedition, I visited the two villages which were involved, Ghavria and Kalovatos, accompanied by my wife, Maria, who is Greek. We spoke to the village priest who had not been there in 1962; we explained who we were and what I had done in 1962. We asked him what had happened in this connection when people came to see him to discuss their projected marriages. “Oh,” he said “no one now remembers much about this matter. It seems that some researchers came from Athens aeons ago. They did all these blood tests and they gave people bits of paper with some results, but no one took any notice of these bits of paper when they were deciding whom to marry”. The experience in the other two studies which I mentioned was similar. It should be noted in this context that selective abortion has been widely practised in Greece with respect to haemoglobinopathies. In Cyprus, the acceptance of selective abortion has been more complete than in Greece.

Since you asked about population studies in connection with Leiden, I was involved in one such study during my time there. Two papers were written with several Dutch collaborators *(Fraser, G R, Volkers, W S, Bernini, L F, de Greve, W B, van Loghem, E, Meera Khan, P, Nijenhuis, L E, Veltkamp, J J, Vogel, G P, and Went, L N: A search for associations between genetical polymorphic systems and physical, biochemical, and haematological variables.* ***Human Heredity, 24:*** *424-434, 1974; Fraser, G R, Volkers, W S, Bernini, L F, van Loghem, E, Meera Khan, P and Nijenhuis, L E: Gene frequencies in a Dutch population.* ***Human Heredity, 24:*** *435-448, 1974).*

Our population of 806 individuals consisted mainly of first-year student volunteers at the University of Leiden. I mention this study because in the first paper, we confirmed the association between serum cholesterol levels and the ABO blood group, which I have already mentioned with respect to the initial finding of this association in Greece five years previously *(Mayo, O, Fraser, G R, and Stamatoyannopoulos, G: Genetic influences on serum cholesterol in two Greek villages.* ***Human Heredity, 19:*** *86-99, 1969).* We also confirmed the well-known association between alkaline phosphatise levels and the ABO blood group. More interestingly, it was shown that blood pressure was very strongly correlated with serum protein and albumin levels and with red cell haematological determinations. Multiple regression and correlation analyses suggested that, in addition, weight was a factor affecting blood pressure. While this is not surprising, interestingly enough, no significant effects remained for cholesterol. I have never understood the significance of the strong association of blood pressure with serum protein and albumin levels and with red blood cell count, haematocrit, and haemoglobin levels. To my knowledge, no studies have been performed to explore these associations further.

PSH. Tell me now a bit more about your time in Leiden.

GF. The opportunity to go to Leiden arose because of my friend, Marcello Siniscalco. I could not stay in Seattle because the basis of my going there was not very clear in the first place, as I have explained. The Chairman of the Department of Medicine did not approve of the idea of my having a permanent position. Marcello had gone to Leiden some years previously, and had created the Department of Anthropogenetica (Human Genetics). I had known Marcello since the time when I had been in the Galton Laboratory in 1957-9, and we had remained on very good terms. He told me that he had to leave Leiden because his future was in New York. He told his colleagues in Leiden that his departure would not give rise to a significant hiatus because of the availability of George Fraser as

a very suitable replacement. It was kind of him to say this; eventually I was offered the job and I was happy to accept.

PSH. What did the job involve? Was it a free hand or were there medical aspects involved as well?

GF. I had had experience in genetical counselling. The University Hospital wanted me to create a counselling clinic and the university wanted me to give lectures in Dutch eventually, but they did not put pressure on me or present me with major demands. The main thrust of my ambition with respect to research was to create a study in Zeeland, the southernmost province of the Netherlands. I wanted to make an analysis of the distribution of inherited disease, and of the contribution of genetical factors to disease in general in the population of Zeeland.

It was a very ambitious project, and it was time-consuming trying to set it up. Unfortunately, it proved not to be practicable because Napoleon Bonaparte had instituted very strict regulations in France and in the Netherlands, which were ruled by his brother, about keeping track of people. If you wanted to move, you had to write an application to leave your district, and then you had to write another application to be registered in the district of your new home. The French do not take these rules very seriously now, but the Dutch were still observing them to the letter in 1971 when I arrived.

A great moral trauma had been inflicted on the Dutch nation during the Second World War because the records of all these applications had not been destroyed and had fallen into the hands of the Gestapo. Details such as religion were noted on the applications so that the Gestapo knew exactly where every Jew in the Netherlands was living. This knowledge, of course, had disastrous consequences. This episode was brought up in every conversation I had with officials about my proposed study of Zeeland. In the end, it was decided that such a study was not permissible, in that the details which I proposed to record could eventually be used for nefarious purposes. Newspaper articles were published about the dangerous plans of the University of Leiden.

At the time, I had a discussion with Victor McKusick who had been approached by the Dean of Medicine at the Memorial University of Newfoundland, who wanted to set up just such a study among the 500,000 inhabitants of the province. To cut a long story short, I resigned from my position in Leiden in October 1973, after a period of less than three years, and went to Newfoundland. On my first day in office, Dean Rusted took me to the provincial medical insurance office in St John’s. He said to the director: “Professor Fraser, whom we have been

discussing, has just arrived. How is he going to work with the medical records which he will need? “What medical records? These medical details are confidential. I cannot possibly share them with Professor Fraser.” Thus, my planned work in Newfoundland ended before it began. A vivid picture of this meeting remains indelibly etched on my mind.

During my two years at the Memorial University of Newfoundland from 1973 to 1975, I was involved in an interesting project on the concentration of common variable immunodeficiency, Hodgkin's disease, and other malignancies including embryonic tumours, in a large Newfoundland family. Because of the fragmentation of the population of Newfoundland into myriad small isolated inbred communities, a structure which would have made the population ideal for the general study which I had planned, an extended family could comprise several thousand individuals.

Before going to Newfoundland, I had been collaborating with the INSERM Unit U88 (Medical Informatics and Biostatistics) at the Pitié-Salpêtrière Hospital in Paris. I had made several visits and I had brought with me a large pedigree compiled by Lionel Penrose, together with his ideas how to make it accessible to mathematical analysis with respect to kinship coefficients, inbreeding and other parameters. Lionel was pursuing his ideas using pieces of string, but the members of INSERM Unit U88 became interested in the matter and developed computer programs for such analyses, including a programme for drawing pedigrees without any limitation of size *(Garçon, C, Landre, M-F, and Valat, M-T: Traitement de généalogies. Revue d’Informatique Médicale 3: 21-32, 1972).*

In 1975 and 1976, I spent several months in Paris and collaborated with the members of the INSERM Unit U88 in an analysis, using the computer programs which they had developed, of the large Newfoundland family of over 3000 individuals of whom more than 1200 were alive and dwelling in adjacent communities, in which a concentration of common variable immunodeficiency, Hodgkin's disease, and other malignancies including embryonic tumours had been found.

This project produced three papers concerning the clinical features of the conditions mentioned and the possibility of the influence of genetical factors, concentrated by inbreeding in their causation. As a souvenir of my collaboration with the Paris group, I was given a large tube containing a beautifully drawn pedigree of the whole Newfoundland family containing more than 3000 members, compiled and drawn by a computer.

Buehler, S K, Fodor, G, Marshall, W H, Firme, F, Fraser, G R, and Vaze, P: Common variable immunodeficiency, Hodgkin's disease, and other malignancies in a Newfoundland family. ***Lancet 1:*** *195-197, 1975.*

Marshall, W H, Buehler, S K, Crumley, J, Salmon, D, Landre, M-F, and Fraser, G R: A familial aggregate of common variable immunodeficiency, Hodgkin disease and other malignancies in Newfoundland. I. Clinical features. ***Clinical and Investigative Medicine 2:*** *153-159, 1979.*

Salmon, D, Landre, M-F, Fraser, G R, Buehler, S K, Crumley, J, and Marshall, W H: A familial aggregate of common variable immunodeficiency, Hodgkin disease and other malignancies in Newfoundland. II. Genealogical analysis and conclusions regarding hereditary determinants. ***Clinical and Investigative Medicine, 2:*** *175-181, 1979.*

As a by-product of this project, a rare variant of superoxide dismutase was discovered in this large family- (*Carter, N D, Auton, J A, Welch, S G, Marshall, W H, and Fraser, G R: Superoxide dismutase variants in Newfoundland--a gene from Scandinavia?* ***Human Heredity, 26:*** *4-7, 1976.*

PSH. George, can I move away from what you might call chronology now and ask a couple of things? The first is your translation of Benno Müller-Hill's book *(Müller-Hill, B: Tödliche Wissenschaft: Die Aussonderung von Juden, Zigeunern und Geisteskranken 1933-1945. Rowohlt Taschenbuch Verlag GmBH, Reinbek bei Hamburg, 1984).* What led to that?

In 1984, Walter Bodmer offered me a job in Oxford because he wanted to set up a cancer genetic clinic there. Walter was a delegate to the Oxford University Press. I do not know exactly how the translation project came about, but I believe that Walter discussed such a translation with the Oxford University Press. A lady from the Oxford University Press asked to see me to discuss this project; she told me that the Oxford University Press was going to employ a professional translator. She then asked me whether I would be interested in reviewing the translation. So, I took the book home; a month later I told the lady that I found the prospect of reviewing the translation rather frightening, and that I would really prefer to translate the book myself.

PSH. You have always had a flair for languages, did that start very early or was it something that you just found yourself picking up as you went along later?

GF. I am coming to realise increasingly that this ‘flair for languages’ is actually very limited. I do not really know any language well, apart from English.

PSH. Well you speak a dozen or so, don’t you?

GF. I think that this word ‘speak’ needs clarification. It is better to say that I have variable speaking, reading, and writing knowledge of several languages. When I travel, I speak French when I am in France, Italian when I am in Italy, German when I am in Germany, and so on. As a small child, I spoke Slovak but I can remember very little of the language. My parents spoke Hungarian at home, and I now speak Hungarian reasonably well. Apart from Ancient Greek and Latin, I have followed formal studies of variable intensity and duration in French, German, Hungarian, Russian and Spanish. I have given lectures in French, Portuguese (during the six months of my life which I spent in Brazil), Spanish and, just once, in German.

I have picked up some knowledge of other languages. I can speak, read and write Italian because I have spent much time working and travelling in Italy. Thus, in 1953, after I finished my degree course in Cambridge, Fisher sent me to Milan for a couple of months to work in Luca Cavalli-Sforza’s department at the Istituto Sieroterapico Milanese; subsequently, I participated in teaching summer courses in Sardinia (1964) and Ferrara (1972). I can speak some Dutch because of the time I spent in Leiden. I spent a few months in Yugoslavia in the nineteen-sixties, doing field studies based both in Oxford and in Seattle, and I could speak Croatian at the end of that time. I can speak Modern Greek reasonably well because I have spent much time in Greece with my wife, Maria, who is Greek; in addition, there were the four months of the field studies in the Arta region in 1962, which I have mentioned.

To return to your question about the book, when I said that I would like to translate it, I did not do so because I have a fluent knowledge of German. Rather, it was because the book interested me, and after studying it with the help of dictionaries and various other reference books, I felt that I could translate it. I have had only limited formal training in German, dating back to my time at Winchester College.

PSH. But you have published a number of papers on ethical aspects and what you might call broader humanistic aspects in relation to genetics, so did you find that that was a book that resonated particularly with how you felt?

GF. Yes. I was very interested in the subject of the book.

Müller-Hill, B: Tödliche Wissenschaft: Die Aussonderung von Juden, Zigeunern und Geisteskranken 1933-1945. Rowohlt Taschenbuch Verlag GmBH, Reinbek bei Hamburg, 1984.

Murderous Science: Elimination by Scientific selection of Jews, Gypsies, and Others Germany 1933-1945. Oxford University Press, 1988.

My translation for the Oxford University Press is a hardback edition. A revised and expanded paperback version, with an afterword by J D Watson, was published by the Cold Spring Harbor Laboratory Press in 1998.

I have indeed written a number of papers relevant to the topics which you have just mentioned. In one of the first of these, published in 1972, I wrote that whatever medical geneticists and genetical counsellors advise and whatever procedures are followed as a result of this advice, this is not going to make any significant difference to the gene pool of mankind.
Fraser, G R: The implications of prevention and treatment of inherited disease for the genetic future of mankind. ***Journal de Génétique Humaine 20:*** *185-205, 1972.*

*Also in: Btesh, S, ed: Recent Progress in Biology and Medicine-
Its Social and Ethical Implications (7th CIOMS Round Table Conference). pp 105-126: Council for International Organizations of Medical Sciences, Geneva, 1972.*

Also in: Bajema, C J, ed: Eugenics: then and now. Benchmark Papers in Genetics (Volume 5): Dowden, Hutchinson, and Ross, New York, 1976.

I think Benno Müller-Hill has a more concerned attitude towards these matters, exemplified by his use of the title *The Specter of Kakogenics* for an addendum to the paperback version of my translation of his book, which was published by the Cold Spring Harbor Laboratory Press in 1998. Benno has used this title elsewhere; we must hope that his fears of political and governmental interference with reproductive choices will not materialise despite the warnings from the past to which he refers.

PSH. One of the things that have happened in recent years is that people have discovered the genes underlying the syndromes that you first described.

GF. Yes.

PSH. That must have been a very satisfying thing to see happen?

GF. Yes, the cryptophthalmos story is quite remarkable. In 1963 and 1964, I was in correspondence with Victor McKusick about the catalogues (Mendelian Inheritance in Man) which he was preparing. He sent drafts to me for my comments. Because of two paragraphs on the 'syndrome of cryptophthalmos' which, as we have discussed, I included in my paper, *Our genetical 'load'. A review of some aspects of genetical variation*. ***Annals of Human Genetics 25:*** *387-414, 1962*. Victor decided on the eponym of Fraser syndrome in the first edition of the catalogues (*Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive and X-linked Phenotypes. First Edition. Johns Hopkins Press, Baltimore, 1966).* In the same year, I published a short account of my findings concerning the 'syndrome of cryptophthalmos' *(Fraser, G R: XX chromosomes and renal agenesis.* ***Lancet 1:*** *1427, 1966).*

It took many years for this eponymous designation to be generally accepted. Much later still, one of the genes whose mutant alleles could lead to the condition when in homozygous form, was given the name of *FRAS1 (McGregor, L, Makela, V, Darling, S M, Vrontou, S, Chalepakis, G, Roberts, C, Smart, N, Rutland, P, Prescott, N, Hopkins, J, Bentley, E, Shaw, A, Roberts, E, Mueller, R,, Jadeja, S, Philip, N, Nelson, J, Francannet, C, Perez-Aytes, A, Megarban,e A, Kerr, B, Wainwright, B, Woolf, A S, Winter, R M, and Scambler, P J: Fraser syndrome and mouse blebbed phenotype caused by mutations in FRAS1/Fras1 encoding a putative extracellular matrix protein.* ***Nature Genetics 34:*** *203-208, 2003).*

In a companion paper, the same gene, *Fras1,* was identified in the mouse *(Vrontou, S, Petrou, P, Meyer, B I, Galanopoulos, V K, Imai, K, Yanagi, M, Chowdhury, K, Scambler, P J, and Chalepakis, G. 2003. Fras1 deficiency results in cryptophthalmos, renal agenesis and blebbed phenotype in mice.* ***Nature Genetics 34:*** *209-214, 2003).*

Thus, this gene, *FRAS1*, and its homologues exist in Man, in the mouse, and, according to the website www.ensembl.org, in 200 other species. There have been several other articles published between 2003 and 2005 in *Nature Genetics, Proceedings of the National Academy of Science*, and *Human Molecular Genetics* by Peter Scambler, Ian Smyth and their groups, together with collaborators in Greece and other countries, concerning the genetics and molecular biology of the Fraser syndrome. I have been in touch in recent years with Peter Scambler with respect to the location in *Homo sapiens* of the genes involved—*FRAS1* on chromosome 4 (found in 202 species), *FREM1* (FREM standing for 'FRAS1-related extracellular matrix') on chromosome 9 (found in 49 species), *FREM2* on chromosome 13 (found in 45 species),, *FREM3* on chromosome 4 (found

in 29 species),, and *GRIP1* (GRIP standing for 'glutamate receptor interacting protein') on chromosome 12 (found in 197 species).

A review article concerning the genetics and molecular biology of the syndrome, and of its homologues in the mouse, by Ian Smyth and Peter Scambler *(The genetics of Fraser syndrome and the blebs mouse mutants.* ***Human Molecular Genetics 14 (Review Issue 2):*** *R269-R274, 2005)* has been reprinted in *Fifty Years of Human Genetics: a Festschrift and Liber Amicorum to celebrate the Life and Work of George Robert Fraser (editors Mayo O and Leach C), Wakefield Press, Kent Town, South Australia, 2007, pp 170-177*.

In 1988, Willie Reardon contacted me and asked me to provide information which would enable him and his colleagues to establish contact with the families with X-linked deafness which I had described in a paper published in 1965 *(Fraser, G R: Sex-linked recessive congenital deafness and the excess of males in profound childhood deafness.* ***Annals of Human Genetics, 29:*** *171-196)* and subsequently in my book *(Fraser, G R: The Causes of Profound Deafness in Childhood. A Study of 3,535 Individuals with Severe Hearing Loss Present at Birth or of Childhood Onset (with foreword by V A McKusick). pp 410: Johns Hopkins University Press, Baltimore and London, 1976).*

I gave Willie Reardon this information, and he and his colleagues published several papers about linkage studies with respect to X-linked deafness in ensuing years, using my information in order to include several families which I had seen thirty years previously. It is of some interest to note that when Lionel Penrose had been editor of the *Annals of Human Genetics***,** he had insisted that papers including pedigree data should be accompanied by full details of the members of the families concerned, which were then lodged at the Galton Laboratory. By some miracle, I had retained a photocopy of the details which I submitted with my 1965 paper. This photocopy proved to be of use in tracing these families almost a quarter of a century later. I do not know what has happened to the vast number of such records which were accumulated by Lionel Penrose at the Galton Laboratory.

I was not able to give Willie Reardon such details some years later when he started his extensive studies of the Pendred syndrome, but I was able to give him files which enabled him to trace some of the families which I had studied almost forty years previously *(Fraser, G R, Morgans, M E, and Trotter, W R: The syndrome of sporadic goitre and congenital deafness.* ***Quarterly Journal of Medicine 29:*** *279-295, 1960;Fraser G R: Association of congenital deafness with goitre (syndrome of Pendred: a study of 207 families.* ***Annals of Human Genetics 28:*** *201-249, 1965).*

Willie Reardon and his colleagues have included me as a co-author of a paper connected with the locus responsible for the Pendred syndrome; this was published in 1997, forty years after I presented my PhD thesis on the condition *(E, Coyle, B, Armour, J A L, Coffey, R, Grossman, A, Fraser, G R, Winter, R M, Pembrey, M E, Kendall-Taylor, P. Stephens, D, Luxon, L M, Phelps, P D, Reardon, W and Trembath, R: Pendred syndrome: evidence for genetic homogeneity and further refinement of linkage.* ***Journal of Medical Genetics 34:*** *126-129, 1997).*

In the same year, Willie Reardon showed great generosity in writing a paper entitled *Historical note: Dr George Fraser. (****Journal of Audiological Medicine 6:*** *185-189, 1997).* In this paper, he discussed my past contributions to medical and human genetics, especially in connection with the Pendred syndrome.

I have not had contacts with the many researchers who have investigated the complex situations regarding the loci responsible for the various forms of the Usher syndrome and of the Waardenburg syndrome. And there is, of course, the syndrome of Jervell and Lange-Nielsen and the many loci responsible for related forms of cardiac conduction defects without deafness. In any event, I am very pleased to have been involved in the earlier descriptive studies which preceded the molecular studies of today and, to some extent, prepared the way for such developments.

In this connection, the syndrome of Jervell and Lange-Nielsen and the many loci responsible for related forms of cardiac conduction defects without deafness, may occasionally lead to sudden unexplained death in infancy (cot death), During our collaborative study of the syndrome of Jervell and Lange-Nielsen, Peter Froggatt and I pointed out in three letters to the editors of *The Lancet* and of *Pediatrics* that such defects of cardiac conduction might be responsible for a proportion of cases of cot death, an entity whose aetiology remains largely undetermined even today. Our letters were published between 1964 and 1967. In recent years, our suggestion has been confirmed by molecular studies, although the proportion of cot deaths due to such a cause remains a matter for speculation.

Fraser, G R and Froggatt, P: Congenital cardiac arrhythmia. ***Lancet 2:*** *648, 1964.*
Fraser, G R and Froggatt, P: Unexpected cot deaths. ***Lancet 2:*** *56-57, 1966.*
Fraser, G R and Froggatt, P: Sudden death in infancy. ***Pediatrics, 40:*** *140, 1967.*

PSH. If you look back and had to pick out one piece of work you are most proud of or that you feel most fond of, which would you choose?

GF. That is a difficult question since there are several such papers and it is impossible for me to choose between them. So, I shall list five, all of which have been mentioned previously.

A
Fraser, G R: Our genetical 'load'. A review of some aspects of genetical variation. ***Annals of Human Genetics 25:*** *387-414, 1962.*

B (a sequel to A)
Fraser, G R and Mayo, O: Genetical load in man. ***Humangenetik 23:*** *83-110, 1974*

C
Fraser, G R, Morgans, M E, and Trotter, W R: The syndrome of sporadic goitre and congenital deafness. ***Quarterly Journal of Medicine 29:*** *279-295, 1960.*

D
Fraser, G R: Association of congenital deafness with goitre (syndrome of Pendred: a study of 207 families. ***Annals of Human Genetics 28:*** *201-249, 1965.*

E
Fraser, G R: The implications of prevention and treatment of inherited disease for the genetic future of mankind. ***Journal de Génétique Humaine 20:*** *185-205, 1972.*

Also in: Btesh, S, ed: Recent Progress in Biology and Medicine-Its Social and Ethical Implications (7th CIOMS Round Table Conference). pp 105-126: Council for International Organizations of Medical Sciences, Geneva, 1972.

Also in: Bajema, C J, ed: Eugenics: then and now. Benchmark Papers in Genetics (Volume 5): Dowden, Hutchinson, and Ross, New York, 1976.

Much the same material is covered in a second paper which I mention because it was written specifically in memory of Lionel Penrose.
Fraser, G R: The long-term genetical effects of recent advances in the treatment and prevention of inherited disease. ***British Journal of Psychiatry 125:*** *521-528, 1974.*

Also in: Proceedings of the Third Congress of the International Association for the Scientific Study of Mental Deficiency The Hague, The Netherlands, 4-12 September 1973. pp 82-90.

I think that my conclusions in this last paper, E, which I have already mentioned—that whatever medical geneticists and genetical counsellors advise and whatever procedures are followed as a result of this advice, this is not going to make any significant difference to the gene pool of mankind, are widely accepted now except by some people on the periphery of genetics who keep on saying that we are causing problems for future generations by promoting the survival of deleterious genes. Does anyone take these people seriously?

PSH. It does come up yes, but no, the fact is that it is unlikely that genetic disorders are ever going to be any more of a major problem than they have been; I think most people would agree with you and in a way that resonates very much with what Penrose always said.

GF. Yes. These matters are discussed extensively in my essay about Penrose which has been published in part *(Fraser, G R: Lionel Penrose as scientist and mentor: recollections and lifelong legacies. In: Penrose: Pioneer in Human Genetics (Report on a symposium held on 12th and 13th March, 1998, to celebrate the centenary of the birth of Lionel Penrose) pp 35-39: Centre for Human Genetics at University College London, 1998).*

Lionel in his Presidential Address at the Third International Congress of Human Genetics in Chicago in 1966 said:

The social and biological values of hereditary differences are continually altering as the environment changes.....At the moment, our knowledge of human genes and their action is so slight that it is presumptuous and foolish to lay down positive principles for human breeding. Rather, each person can marvel at the prodigious diversity of the hereditary characters in Man and respect those who differ from him genetically. We all take part in the same gigantic experiment in natural selection.
(The influence of the English tradition in human genetics in: J F Crow and J V Neel, eds: Proceedings of the Third International Congress of Human Genetics pp.22-23: Johns Hopkins University Press, Baltimore, 1967.)

PSH. That brings me to my last question actually, George, which is whom would you regard as having been the biggest influence on your work and life in medical genetics?

GF. I shall answer your question in two parts. Firstly, in general, I have an equal respect for Fisher and Penrose with respect to their intellectual qualities. Haldane, of course, I would put in the same class, but, as I said, I had very little contact with him during my time at the Galton Laboratory, apart from his Drosophila class.

Hermann von Helmholtz wrote:

Anyone who has once come into contact with one or more men of the first rank must have his whole mental standard altered for the rest of his life. Such intercourse is, moreover, the most interesting that life can offer.

Wer einmal mit Männern ersten Ranges in Berührung gekommen ist, hat seinen geistigen Maassstab für das Leben verändert; zugleich ist eine solche Berührung das Interessanteste, was das Leben bieten kann.

Since meeting Fisher, Haldane and Penrose during the early part of my career, I have not been connected with any one whom I would consider to be their equal in intellectual rank. They have all influenced me to varying extents in my work and life in human and medical genetics. I miss the exquisite pleasure afforded by these early contacts with them—truly the most interesting that life can offer.

I also miss my contacts throughout my career in human and medical genetics with several thousand patients, together with members of their families. They included patients with hearing defects, those with visual defects, those with familial cancer whom I saw in my Cancer Genetic Clinic and elsewhere in Oxford between 1984 and 1997, and others whom I have seen in genetical counselling clinics and in various other contexts all over the world. They have all been my friends; losing touch with them, following my obligatory retirement when I reached the age of 65 years in 1997, has left a large gap in my life.

To return to the influence of Fisher, Haldane and Penrose on my work and life in human and medical genetics, by far my closest personal contact was with Lionel Penrose. I have made this abundantly clear in the essay which I have mentioned. I regarded him not only as a scientist and as my mentor, but also as my friend.

Lionel urged me strongly to accept the offer of the position as Professor of Human Genetics in Leiden, telling me that scholarship was greatly

appreciated in the Netherlands. I took his advice, and I was very pleased to have been able to express my gratitude to him for his guidance and friendship in the course of a tribute which I included in my inaugural lecture as Professor of Human Genetics in Leiden on 29 October 1971 (*Fraser, G R: Profound Deafness in Childhood. A Study in Human Biology. (Inaugural address delivered on his entrance into office as Professor of Human Genetics at the University of Leiden on October 29th 1971) pp 15: Universitaire Pers, Leiden, 1971).* This inaugural lecture was given a quarter of a century after Lionel's own inaugural lecture on becoming Galton Professor of Eugenics in the University of London at University College, a lecture of outstanding quality, which is widely recognised as representing a milestone in the development of human genetics *(Penrose, L S: Phenylketonuria: a problem in eugenics. Lancet 1: 949-953, 1946)*

After an initial introduction to genetics by the late Sir Ronald Fisher, you gave me further training in the science which you have loved so long and served so well. To you, I owe above all a small insight into the exacting observances and rigorous laws of scientific method. I should like here to express my gratitude to you and to acknowledge my debt. As a geneticist, you have always had a keen professional interest in human variation and I have learnt to admire your great tolerance and understanding of the foibles and weaknesses to which this can give rise. The discipline of Human Genetics affords a scientific basis for the aphorism of Terence which applies so fittingly to you.

Homo sum; humani nil a me alienum puto.
I am a man; there is no part of the human condition which lies outside my concern. Publius Terentius Afer (Terence)

In an unforeseeable way, there was a response to this tribute thirty-five years after Lionel's death in 1972. I have mentioned the book *Fifty Years of Human Genetics: a Festschrift and Liber Amicorum to celebrate the Life and Work of George Robert Fraser (editors Mayo O and Leach C), Wakefield Press, Kent Town, South Australia*, which was published in 2007 on the occasion of my 75th birthday.

Two of Lionel's children contributed to the Festschrift and *liber amicorum,* his daughter, Shirley Hodgson, and his son, Oliver Penrose.

In the dedication to her contribution *(BRCA1 and BRCA2: Breaking the cycle and repairing the damage pp 118-125)*, Shirley wrote:

George was a good friend of my father, Lionel Penrose, and they worked together fruitfully at a time when human genetics was rapidly developing, exchanging ideas and enthusiasm. George has gone on to develop his work with great success. Lionel would have liked to add something to this, with words of appreciation for this friendship and collaboration.

This dedication gives me great pleasure.

PSH. George, thank you very much.