

# BIOGRAPHICAL MEMOIRS

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## **Ruth Ann Sanger. 6 June 1918 – 4 June 2001**

Nevin Hughes-Jones and Patricia Tippett

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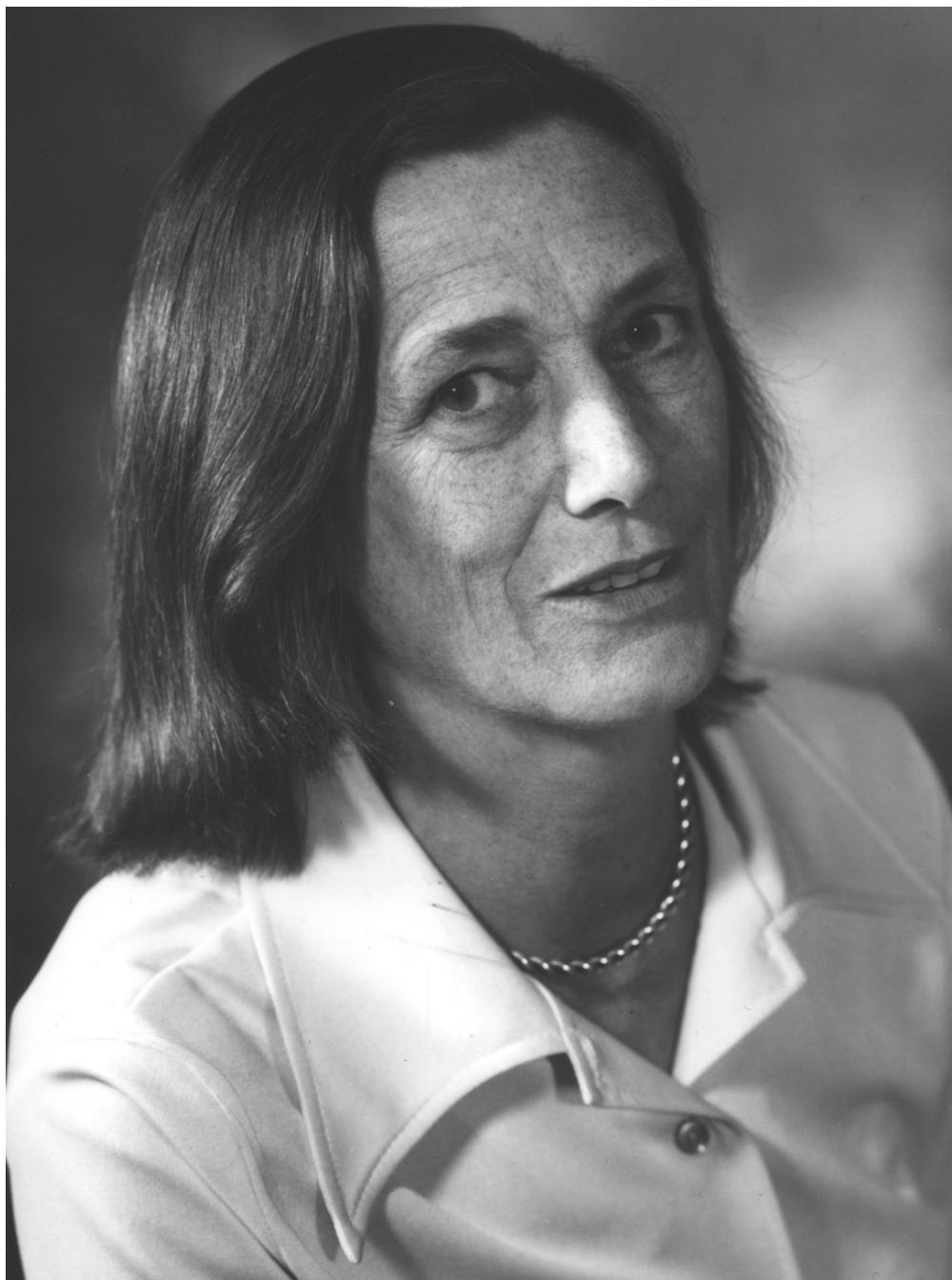
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RUTH ANN SANGER

6 June 1918 — 4 June 2001



*Ruth Sanger*

## RUTH ANN SANGER

6 June 1918 — 4 June 2001

Elected FRS 1972

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Ruth Ann Sanger's scientific career was concerned with the delineation and mapping of human blood group genes by simple manual methods using, as tools, blood group antibodies and the agglutination reaction followed by statistical analysis of the results. Her active period coincided with the flowering of the whole subject of blood groups, which was initiated by the recognition of the clinical significance of the Rh antigens and the rediscovery of the antiglobulin reaction by Coombs, Mourant and Race (Coombs *et al.* 1945). In these days of 'high-technology' research, it is salutary to recognize that the complex body of knowledge that has been accumulated about blood groups has been derived by using the very simple technique of the visible cross-linking of red cells by antibodies specific for the blood group antigens present on the red cell surface. Landsteiner had by chance discovered the ABO blood group system in 1900 with the use of the agglutination reaction, but little progress was made in the next 45 years and we now know that the main reason for this is that most blood group antibodies are not physically capable of bringing about the cross-linking and agglutination of red cells on their own. This problem was solved by the introduction of the antiglobulin reaction, which uses a secondary antibody to bring about the cross-linking of blood group antibodies already attached to red cells.

### FAMILY AND EARLY YEARS

Ruth Sanger's father was the Rev. Hubert Sanger, born in London in 1881, the youngest of five sons (John, William, Frederick, Edward and Hubert) and one daughter (Mary) born to her grandfather, William Albert Sanger (1840–83) and her grandmother, Ann Mary (*née* Hoff, 1837–1913). Hubert studied at St John's College, Cambridge, and was President of the University Boat Club in 1905. He was ordained in 1905 in Rochester Cathedral and while

curate in nearby Strood he met Ruth's mother, Katherine Mary Ross Cameron, who was visiting from Australia. Hubert went out to Australia in 1908 and on the way there visited his brother Frederick (father of Fred Sanger FRS), who was a medical missionary in China. Hubert married Katherine in 1909 and was then given a parish in the west of Queensland. He was later persuaded to leave the 'bush' and turn to school teaching in Sydney, first as house-master at Kings School, Paramatta, and finally as headmaster of the celebrated school Armidale. On her mother's side, her grandfather was Donald Cameron (1838–1915) of the Isle of Skye. After graduating from Edinburgh University he travelled to Queensland to be a tutor, and on the ship he met Martha Smith, the daughter of a doctor at Winchcombe; they were married in 1860. Donald and Martha had four sons (Alexander and Donald took up medicine, Walter became a mining engineer, and Archibald a hydraulic engineer) and one daughter, Katherine (born in Queensland in 1878), who married Hubert.

Ruth had three siblings, two brothers and a sister. Her home was always attached to a boys' school; her parents also had a very simple remote seaside home where the whole family would gather for all school holidays, each of the four children being allowed to bring two friends. 'These holidays were remembered with great joy, my parents allotting set jobs for boys and for girls and the rest was all adventure on the seashore and lakes. I think that it was the friends of my older sister and brothers who persuade me to do science at University.'\*

Ruth attended three schools in New South Wales: Harleyville Ladies College (1924–26), New England Girls school, Armidale (1926–27), and Abbotsleigh Wahrounga (1928–35). Ruth's journey from Armidale to Abbotsleigh took a day on the train and she would tell tales of swollen rivers and exciting journeys. She then went to Sydney University, as the family had sufficient funds to allow each of the four children to have three years post-school training. She chose science 'since my sister found Arts too difficult'. She found the first year hard work, especially because she had not studied physics or chemistry at school; although Abbotsleigh was an academic school it did not teach 'unlady-like subjects like Physics or Chemistry'. In the second and third years she studied physiology and zoology as main subjects 'because I could understand and enjoy it'. She achieved a distinction in her final year and was awarded the Haswell Prize and G.S. Caird Scholarship for zoology, and then went on to do an honours year. Her thesis was on the subject of the stomach contents of elasmobranch fishes and she achieved second-class honours.

#### POST-GRADUATION ACTIVITIES

On graduation, she was persuaded by a friend to take a temporary post in the haematology laboratories of the Children's Hospital at Camperdown in Sydney, which she realized 'was a good type of job for me' and then took a post on the scientific staff of the NSW Red Cross Blood Transfusion Service (Director, R.J. Walsh) initially to work on drying blood plasma, a project of great importance to the war effort. After two years she moved to a small blood-grouping laboratory and found the work very satisfying. It was just at that time that news of the development of the Rh system had arrived in Australia and as a result 'she was free ... to deal with the fascination of the complexities of Rh'. Ruth's great asset that motivated her scientific career was this intellectual fascination concerning the nature of blood groups and of their

\* Remarks in quotations are taken from rough notes found among Ruth Sanger's papers.

interrelations. She was fortunate in the fact that the discovery of the Rh system was the start of the expansion of our knowledge about blood groups. There are now at least 29 known independent systems, and over the decades she became involved with many of them.

Sanger had a strong desire to come to England to study and obtain further experience; Walsh therefore arranged for her to work with R.R. Race (FRS 1952), who suggested that she should join the Medical Research Council (MRC) Blood Group Research Unit at the Lister Institute of Preventive Medicine. She sold her only asset, the family piano, and travelled on one of the first postwar ships to carry passengers, arriving in England in August 1946, at a time that coincided with the establishment of the Blood Group Research Unit. The Unit was given the task of studying the 'inheritance of human blood groups and their applications to problems of human genetics'. The MRC had also established the MRC Blood Group Reference Laboratory under Dr A.E. Mourant (FRS 1966), which was also concerned with the theoretical and practical aspects of blood groups and with the provision of reagents for the National Blood Transfusion Service. Both Units were housed in the Lister Institute in the Chelsea Bridge Road in London, which was also home to Professor Walter Morgan (FRS 1949) and Dr Winifred Watkins (FRS 1969), who were working in the Biochemistry Department on carbohydrate antigens with special reference to the ABO blood group system. There was thus a substantial core of research workers at the Lister centred on blood groups; the Blood Products Research Unit, jointly run by the Lister Institute and the MRC, was also active at the Lister.

Soon after her arrival in London, the decision was made that the work she performed would be submitted for a PhD thesis in the University of London and she therefore obtained additional funds and an extra year's absence from Sydney for this purpose. The subject of the thesis was ambitious and was concerned with all the blood group systems that were known at the time; the title was 'The multiplicity of blood group systems'. At that time there were seven well-established systems: ABO, MN, P, Rh, Lutheran, Kell and Lewis. All seven systems were discussed in the thesis, but Sanger's most substantial contributions were in the MN and Rh systems.

The most important discovery during this period was the finding of an additional antigen, S, associated with the MN system (4)\*. Walsh in Sydney came across a patient's serum with an unidentified antibody and in March 1947 sent it to Sanger at the Lister. The investigation of this antiserum was performed by a method that had become routine in the Unit, namely the application of simple mathematical analyses to the results of the agglutination patterns of the antiserum. The Unit had developed the habit of applying Fisher's  $2 \times 2$  contingency tables to the results whenever an unknown antibody was investigated. This method of statistical analysis then gave the probability of the new antigen's being related to or independent of a 'known' blood group system. Its use on the Walsh antiserum showed that the antigen was related to the MN system and Sanger named it S. In addition, she made a survey of MNS frequencies in a number of different populations, initially Bostonians and later Latvians, altogether a total 474 people (3).

Her initial interpretation of the results suggested that there were four alleles, *M*, *MS*, *N* and *NS*, but she did put forward the alternative suggestion that S might be the product of a separate gene, the MNS system being similar in organization to that of the Rh system; and she also postulated that there could be an allele *s*. If this were to be so, she predicted that the *MN* genes

\* Numbers in this form refer to the bibliography at the end of the text.

would be located very close to *Ss*, otherwise crossing-over would have resulted in the ratio of *MS* to *Ms* being equal to that of the ratio of *NS* to *Ns*, which it was not. Fifty families were studied and it was shown that the inheritance was Mendelian. It was finally established some 15 years later that this interpretation was the correct one and that the *Ss* locus is separate from *MN* but so closely positioned that only three examples of cross-over in 123 families were found.

Sanger investigated the P system, described in 1927 by Landsteiner and Levine, by studying 50 families for the inheritance pattern of the antigen and calculating the gene frequencies. Contingency tables showed that there was no relation to any other known blood group system. Several years later (7), she played a seminal role in the expansion and elucidation of the antigens within the P blood group system.

Sanger then turned her attention to the Rh system, which had been described only a few years earlier in 1941. On arrival in the Blood Group Unit, she became involved in an important project to determine the gene frequencies of the various components of the Rh system in the UK. Race and Fisher had postulated that there were three allelic pairs of genes, *Cc*, *Dd* and *Ee*, all closely linked on the chromosome and could be assembled in eight different ways, namely *Cde*, *cDE*, and so on. It was postulated that the eight different groupings had arisen by the process of 'crossing-over'. The findings of the Blood Group Unit's project (2) were fully consistent with this proposal and established the essential correctness of the Race-Fisher analysis.

Sanger had written an earlier paper on the Rh system that was based on work done in Sydney; it is very revealing of her method of working and of her analytical approach. Throughout her career, quantification of the data using simple mathematical methods was one of her strong points and a key to her success, and this is demonstrated in this paper (1). In the Rh system many antibodies would not agglutinate red cells and, before the introduction of the antiglobulin test, revealed their presence by their ability to block agglutinating antibodies. It was not at all clear what the mechanism of blocking was at that time, and to get some insight into the problem she measured the blocking ability over a wide range of concentrations and established that the phenomenon was not dependent on concentration; she interpreted this as suggesting that both agglutinating and blocking antibody combined with a common Rh receptor, an interpretation upheld by subsequent studies.

In addition to these systems, Sanger also made contributions to the Lewis system, which had been discovered by Mourant in 1946 and in which two antigens,  $Le^a$  and  $Le^b$ , were recognized. Sanger had four anti-Lewis sera available to her; however, the agglutination patterns were complex and interpretation of the data was difficult and she stated that 'the problem was not yet solved'. Later, she and Race continued to work on the system, particularly on the observation that parents of  $Le(a+)$  persons could both be  $Le(a-)$ , which had led them to propose the theory that  $Le(a+)$  was a Mendelian recessive character. The truth of this theory was investigated by the study of 79 families. Sanger calculated the expected incidence of  $Le(a+)$  and  $Le(a-)$  children that would occur from a variety of  $Le(a+)$  and  $Le(a-)$  matings; the observed frequency was found to agree closely with that predicted.

In the final chapter of the thesis, Sanger discussed the multiplicity of the known blood groups and their interrelations. She pointed out that the seven well-established independent blood group systems (ABO, MNS, P, Rh, Lutheran, Kell and Lewis) resulted in a potential for  $1.1 \times 10^7$  theoretically possible genotypes and thus put forward the concept of the individuality of humans as far as human blood groups were concerned. This is illustrated by the finding that with the antisera available to her, she was able to recognize about 10 300 different blood

group phenotypes; in a group of randomly selected people that she investigated there were 179 different blood group combinations; 133 of these were unique, foreshadowing Medawar's concept of the uniqueness of the individual. In the summary, Sanger stated, 'The study of blood group systems are of fundamental importance in the field of human genetics.... Blood group antigens are closely related to the genes that give rise to them.... The study of these antigens is the closest approach yet possible to the study of the genes themselves which surely must be one of the most fundamental of biological enquiries.' It was this realization that she was elucidating the structure and organization of the genes that she found so fascinating and which was the motivation for her work.

The thesis was submitted and the degree awarded in early 1949. After the completion of the PhD thesis, Sanger returned to Sydney as originally planned to complete her contract with the Red Cross Blood Transfusion Service, but returned to the Blood Group Research Unit in 1950.

It is clear in retrospect that both Sanger and Robert Race had been planning for some time to write a book on the subject of human blood groups, and in August 1950 the first edition of *Blood groups in man* appeared. The structure of the book was based on Sanger's PhD thesis and was concerned with the same blood group systems, with the addition of the Duffy system, which had been described only after the thesis was completed. The literary style of the book is delightful; as R.A. Fisher commented in the Preface, 'It is fortunate that the authors can command a simple and lucid style, for much that is to be expounded is really intricate'. There is much wit throughout, such as 'some of the possible genotypes must be so rare that they may never have formed the blood of an Englishman'.

As knowledge of the groups advanced rapidly, five more editions followed, until the last appeared in 1975; the text progressively increased in length. The book was virtually the only comprehensive account of the subject available during that period; it had no rival and was read by all those working in the field throughout the world. By the time the last edition appeared, the number of blood group systems had risen to 16 and included over 160 identifiable antigens. It was this great increase in the size of the subject that finally brought the project to an end. The first sentence in the Preface of the 6th edition reads, 'Here is the last edition of this book: the subject has grown to need more than our two pencils'.

Sanger contributed to the description and expansion of most of the known blood group systems. Many insights came from studying unusual phenotypes. In the ABO system a new phenotype was reported in which both cells and serum were unusual; the cells were not agglutinated by anti-A, anti-B, anti-H or anti-O, and the serum contained anti-A, anti-B and anti-H (5). The three initial examples studied came from Bombay, so the phenotype was called the 'Bombay' phenotype. Elucidation of the chemical structures of A, B and H antigens by the groups of Witebsky, of Morgan and Watkins, and of Kabat, and investigation of the Bombay phenotype contributed to the understanding of the biosynthetic, and thereby the genetic, pathways of the ABO antigens.

Individuals who were classified as U-negative were also found to be S-negative, s-negative, a previously unknown phenotype; this finding showed that the U antigen belonged to the MNSs system. S- s- U- samples were found in Afro-American populations but not in those of European ancestry (6). A more important observation was the recognition by Sanger that the Tj(a-) phenotype belonged to the P system (7). This led to a renaming of the original antigen as P<sub>1</sub>; the second, more basic, antigen was called P. The third antigen, P<sup>k</sup>, was also identified by Sanger as the result of receiving red cell samples from unrelated Finnish families. Equally importantly, she suggested that the known facts about the P system could be

interpreted along the well-known lines of the  $A_1A_2BO$  relationship but could not suggest a genetic pathway that would fit all the facts.

Sanger's work also expanded the Rh system, which became very complex. She recognized the deleted Rh phenotype,  $-D-$ , and this was followed by descriptions of  $cD-$  and  $C^wD-$  phenotypes and, most excitingly, by cells that seemed to lack all Rh antigens,  $Rh_{null}$  (8). Although these and many other findings did not fit comfortably with the three-loci theory, observations were faithfully recorded to provide facts for future workers. Studies of other Rh problems revealed many low-incidence Rh antigens. By the last edition of *Blood groups in man* in 1975, Rh had at least 35 recognized antigens and Sanger had contributed to the understanding of many of them. More importantly, she deduced the genetics of the LW system and showed that LW antigen was not controlled by the *Rh* locus.

Sanger contributed to the expansion of the Kell and Lutheran systems. She also identified the dominant inhibitor of the Lutheran antigens and recognized its inhibitory effect on the genetically independent  $P_1$  antigen. From her studies on secretions she showed that anti-H was found in the serum of  $Le(a+b-)$  individuals. Although not involved in the initial work on the Duffy system, she found that the phenotype lacking both Fy antigens,  $Fy(a-b-)$ , was not uncommon in people with African ancestry. Study of clinically significant antibodies that caused transfusion problems revealed a null phenotype in the Kidd system. Samples lacking other high-incidence antigens not belonging to any of the known blood group systems were also studied; most, with the help of biochemical studies, have now formed the basis for additional systems. Sanger contributed to understanding the variable-strength antigen called  $Sd^a$ . She recognized that the *Dolichos biflorus* lectin, used as anti- $A_1$  in routine blood grouping, agglutinated all  $Sd(a+)$  samples regardless of ABO phenotype and that the reaction, like the reaction with  $A_1$  cells, was inhibited by *N*-acetylgalactosamine (10). This suggested that  $Sd^a$  antigen, like A antigen, depended on a terminal *N*-acetylgalactosamine; this finding was later confirmed by the isolation of the  $Sd^a$  determinant by the biochemists. She emphasized the need to do family studies and, if possible, to look at frequencies in different populations. Although her studies often did not answer all questions, they provided material for biochemists and DNA workers to investigate.

The most dramatic and exciting discovery concerning blood group systems was that of placing the  $Xg^a$  gene on the X chromosome by the Blood Group Research Unit in 1962, and this event was to dominate Sanger's activities for the next 20 years. The origins of this discovery are delightfully described in a short account written in *Vox Sanguinis* retrospectively in 1983 (11):

In the summer of 1961, we received a sample of blood from a Mr And— suffering from telangiectasia in the Butterworth Hospital, Grand Rapids.... We were busy finishing the 4<sup>th</sup> edition of *Blood Groups in Man*, so our assistants tested the serum, which clearly had a new antibody.... Eventually ... we said ... 'on Saturday we shall look at the results...' On Saturday the first striking result was that the families did not exclude association with sex.... When one of us came back from shopping she immediately asked what was the antigen frequency in the two sexes and this precipitated frantic counting of the random series whose sex we could remember. The count showed that the antigen was more frequent in the females than in the males. This strongly suggested that a dominant X-linked character was operating and the segregation of the antigen in the families was seen to be consistent with the rules of X-linked dominance. On Saturday ... at a party in Dr Mourant's house the sexes of some more of the English donors were recollected and Professor van Loghem and some of his staff from the Netherlands Red Cross Transfusion Service in Amsterdam ... were able to remember the sexes of most of a series of Dutch donors.... The excess of females over males having the new antigen became beyond question.

Now that the entire sequence of the genome is known, it is difficult for us to empathize with the intellectual excitement that accompanied this finding. The description of a new blood group gene and its simultaneous assignment to a chromosome was quite unique and the occasion for understandable pleasure. The details of the investigation appeared in *The Lancet* in 1962 and showed the inheritance of the antigen Xg<sup>a</sup> in 50 Caucasian families with 104 children. The authors stated that 'there are certain rules that must be laid down for an X-borne dominant antigen', which they enumerated and went on to report that 'the good fit of the families to the expected frequencies, their complete concordance with the quite elaborate rules of sex-linkage, and the different distribution of the antigen in the two sexes (males, 62%; females, 89%) established the X-linkage of the new character so surely, in our opinion, that we stopped testing random people and normal families'.

The final section of the paper discussed the interesting consequences that followed the demonstration of the sex-linkage of the antigen, namely, 'the antigen may play a leading part in helping to plot the relative positions of genes on the X chromosome' and also the elucidation of the congenital abnormalities, such as Turner syndrome (phenotype XO) and Klinefelter syndrome (phenotype XXY). Race and Sanger's findings consolidate much of what was previously known about sex-linkage and the paper ends with this tribute to others: 'During the course of this investigation we have learned to appreciate more fully the very beautiful solution of the problem of sex-linkage worked out long ago on much more difficult material than ours'.

#### APPLICATIONS OF BLOOD GROUPS TO HUMAN GENETICS

It can be said that the dominating activity of the Blood Group Unit concerned the contribution of blood groups to gene mapping. When a new red-cell antigen was identified, families were studied to show whether the encoding gene was controlled by a known system or represented a new system. Linkages were sought between blood group systems as well as to genes for diseases. Linkages were established when two markers travelled together through the generations; occasionally they separated as the result of the 'crossing-over' of chromosomes. The frequency of 'crossover offspring' can be used to determine the distance separating the markers.

The tools for the detection of linkages involving the analysis of families were developed by a number of mathematicians and 'they were polished and waiting for the data that they deserved.... Fortunately for the non-mathematician it is not necessary to understand the tests.... A great service was done to us innumerable by mathematicians who gave recipes for the application of *u* statistics ... and lod scores...'. The *u* statistics of Fisher and Finney were replaced by the lod scores of Maynard Smith *et al.* (1961) and then by the computer program LIPED; these tools were introduced into the Unit by Sanger. The lod scores (log probability ratios) are based on the ratio of the number of recombinants to non-recombinants and the actual score is obtained from statistical tables. Some of the intellectual excitement that accompanied the analysis of probabilities is seen in Race and Sanger's account of drawing graphs to show linkages. They state in *Blood groups in man*, 'as families roll in it gives great pleasure especially when a mere molehill grows into a mountain'. Race and Sanger thought that blood groupers should have the pleasure of analysing their own results, so they included, with the authors' permission, a simple explanation and a table of scores with corrections for the double backcross mating type (the most informative mating) in their 5th and 6th editions of *Blood groups in man*.

Red-cell antigens, partly because of their ready availability, were initially the most useful class of chromosome markers used for linkage investigations, and up to 1966 blood group markers provided all the autosomal linkages and the 1975 6th edition lists 11 possible or established linkages up to 1974. A disadvantage of red cell groups is that tests determine phenotypes that often represent more than one genotype, so the study of red-cell antigens has been replaced by DNA technology.

In the early work on X-chromosome linkage, there was a considerable amount of euphoria that, once an X-linked marker of useful frequency was found, 'measured linkages would follow thick and fast'. This was not to be and, as they observed rather wistfully in *Blood groups in man*, 'our Unit ... have learnt how surprisingly hard it is to establish linkage between loci even when they are known to be carried on the same chromosome'. Nevertheless, substantial progress was made. The Unit was recognized as the world's leading laboratory on the subject, and blood samples flowed in; as a result, Sanger was a co-author on almost a quarter of the papers published on the subject that were quoted in *Blood groups in man*. By the time of the publication of the 6th edition, the linkage had been firmly established between Xg and the genes for three diseases, namely X-borne ichthyosis, ocular albinism and retinoschisis; there were also 11 instances of possible linkages. They pictured the position of the Xg locus to be near the end of the short arm of the X chromosome and although they accepted that their reasons for this position were 'frail', we now know that their assumption was correct. After Sanger's retirement in 1983, the Unit continued to work on the problem until it closed in 1995; the study of various blood samples submitted to it during that period contributed to the identification of a candidate gene, *PBDX*, as the Xg gene. The *PBDX* gene straddles the pseudoautosomal boundary and thus all genes beyond this point would not behave as X-borne. As Race and Sanger surmised, the terminal position 'would be wasting half its surveying power on thin air', thus accounting for the rather disappointing shortage of proved linkages.

In recognition of her work on the Xg system, Sanger was given the co-chairmanship of the X chromosome committee of the Human Gene Mapping Workshop, an official body organized under the auspices of the National Foundation, March of Dimes, and she held this position at Human Gene Mapping 2, Rotterdam Conference (1974) with P.L. Pearson and J.A. Brown, and at Human Gene Mapping 4, Winnipeg Conference (1977) with O.J. Miller and M. Siniscalco. The deliberations of the Workshops were published in *Birth defects: original articles series* and also in *Cytogenetics and Cell Genetics*.

Another area in human genetics that the discovery of Xg opened up was the determination of the origin of the X chromosome in X aneuploidy. Polani *et al.* (1956) used red-green colour blindness for this purpose but the Unit realized that the 'more useful' frequencies of the Xg groups 'made the data vastly more informative'. The abnormality can arise either at the first or second division of spermatogenesis, at oogenesis or at a post-zygotic stage, and consists of the non-disjunction of X chromosomes. The investigation was truly an international collaborative exercise, samples of blood being sent from over 100 physicians or cytogeneticists, mainly from Europe. Their insights into the possible mechanisms involved allowed them cleverly to conclude from the data the following. (i) It had always been assumed that XXY could arise through an accident at spermatogenesis, and they provided the first proof in humans that this was so. (ii) Where the two Xs of XXY resulted from maternal non-disjunction, it was shown that there was heterogeneity of the mechanisms; that is, the Xs were either two different Xs, one from each maternal grandparent, or duplicates of one of the mother's Xs. (iii) By

a similar analysis it was possible to show mechanisms of similar oddities, such as XXXY, XXXXY, XXY/mosaics and XX males and a whole host of other XY abnormalities. A Finnish family of an XXYY propositus provided the first evidence in humans that non-disjunction at consecutive meiotic divisions is possible. As Race and Sanger said, ‘the Xg groups have made a good contribution in the field of sex-chromosome aneuploidy’.

A further aspect of the physiology of the X chromosome to which the Xg group contributed was the Lyon hypothesis, which had postulated that one of the two X chromosomes in each somatic cell of the female is inactivated at a very early stage of development. As evidence for the theory grew, there remained the subsidiary question of whether it involved all the loci on X. If it involved Xg, then in the  $Xg^aXg$  female half the red cells should be Xg(a+) and half Xg(a-). There were technical problems involved in demonstrating this, and there was no proof that Xg<sup>a</sup> was intrinsic to red cells. However, it was finally solved and a paper in *The Lancet* from the Unit recounted how separable amounts of both Xg(a+) and Xg(a-) cells were found in the circulation of chimaeras (9). Thus Xg, on a normal X, was the first locus that was found not to be involved in inactivation.

Other fruitful fields of study were chimaeras (derived from two or more zygotes) and mosaics (derived from a single cell lineage). Chimaeras were divided into twin chimaeras, in which two cell lines are present but only in the blood, and dispermic or tetragametic chimaeras, in which two cell lines are present both in blood and in other tissues. Although not as dramatic as information given by biochemists and cell hybridizers, they made a useful and sometimes essential contribution to human genetics.

#### RETIREMENT

In 1983, Sanger retired and although she continued to be interested in the work at the Blood Group Unit, she gradually withdrew from professional commitments. She firmly rejected all invitations to lecture but pursued other interests, attending classes on architecture and geology, and keeping fit. She also enjoyed visiting friends and relations in Australia for three months during the winter every other year; she always preferred the warmth and sunshine to English winters.

Ruth Sanger’s character can be described as ebullient—full of cheerful excitement and enthusiasm. She kept many of her Australian characteristics: she was very friendly and interested in people but not over-awed by her seniors nor condescending to her juniors, and always approachable. She was hard-working, but even serious work and discussions were enlivened by humour and shared laughter. She was modest about her abilities and gratefully acknowledged contributions and help from colleagues. Despite her quick intelligence she remained nervous of giving lectures. Through her work and attendance of meetings she made many friends worldwide within the genetics and blood grouping fields.

The close association of Rob Race and Ruth Sanger, both fascinated by the complexity of the whole subject of blood groups, led to their marriage on 6 April 1956, which proved to be a highly successful relationship. Their careers neatly spanned the extraordinary flowering of our modern knowledge of blood groups, which dates from the discovery of the Rh system in the early 1940s to the initiation of the elucidation of the structure of the genes in the 1980s. Although so many people were involved in collecting the ‘shells’ (*Blood groups in man* quotes over 3000 references), nevertheless the phrases ‘human blood groups’ and ‘Race and Sanger’

were almost synonymous. They were the central axis around which the subject was coordinated and revolved on a worldwide basis. Such a relationship between authors and subject must be almost unique in the scientific world. Ruth Sanger was elected to the Fellowship of The Royal Society in 1972, to join her husband, until his death in 1984, as one of the small band of husband and wife Fellows.

#### HONOURS

- 1957 Karl Landsteiner Memorial Award, USA (jointly with R.R. Race)
- 1970 Philip Levine Award, USA (jointly with R.R. Race)
- 1972 Fellow of The Royal Society  
Gairdner Foundation Award, Canada (jointly with R.R. Race)
- 1973 Oliver Memorial Award for Blood Transfusion, British Red Cross
- 1990 Doctor of Medicine (*honoris causa*) of the University of Helsinki

#### MEMBERSHIP OF SOCIETIES

- 1957 Honorary Member, Sociedad de Hematologia del Instituto Mexicano del Seguro Social
- 1971 Honorary Member, Ontario Antibody Club
- 1972 Corresponding Member, Deutsche Gesellschaft für Bluttransfusion
- 1973 Honorary Member, Norwegian Society of Immunohaematology
- 1975 Honorary Member, International Society of Blood Transfusion
- 1996 Honorary Member, British Blood Transfusion Society

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The frontispiece photograph was taken in 1972 by Argent, and is reproduced with permission.

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The following publications are those referred to directly in the text. A full bibliography appears on the accompanying microfiche, numbered as in the second column. A photocopy is available from The Royal Society's Library at cost.

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|------|-------|------|---|
| (1)  | (3)   | 1946 | The incomplete antibody: a quantitative aspect. <i>Nature</i> <b>158</b> , 487.   |
| (2)  | (6)   | 1948 | (With R.R. Race, A.E. Mourant & S.D. Lawler) The Rh chromosome frequencies in England. <i>Blood</i> <b>3</b> , 689–695.   |
| (3)  | (11)  | 1948 | (With R.R. Race, S.D. Lawler & D.V. Keetch) Blood groups of Latvians, A <sub>1</sub> A <sub>2</sub> BO, MN and Rh. <i>Ann. Eugen. (Lond.)</i> <b>14</b> , 134–138.                  |
| (4)  | (14)  | 1948 | (With R.R. Race, R.J. Walsh & C. Montgomery) An antibody which subdivides the human MN blood groups. <i>Heredity</i> <b>2</b> , 131–139.  |
| (5)  | (33)  | 1952 | (With Y.M. Bhende, C.K. Deshpande, H.M. Bhatia, R.R. Race, W.T.J. Morgan & W.M. Watkins) A 'new' blood group character related to the ABO system. <i>Lancet</i> <b>i</b> , 903–906. |
| (6)  | (45)  | 1954 | (With T.J. Greenwalt, T. Sasaki, J. Sneath & R.R. Race) An allele of the S(s) blood group genes. <i>Proc. Natl Acad. Sci. Wash.</i> <b>12</b> , 1126–1129.                          |
| (7)  | (50)  | 1955 | An association between the P and Jay systems of blood groups. <i>Nature</i> <b>176</b> , 1163–1164.   |
| (8)  | (90)  | 1961 | (With G.H. Vos, D. Vos & R.L. Kirk) A sample of blood with no detectable Rh antigens. <i>Lancet</i> <b>i</b> , 14–15.   |
| (9)  | (169) | 1971 | (With J. Ducos, Y. Marty & R.R. Race) Xg and X chromosome inactivation. <i>Lancet</i> <b>ii</b> , 219–220.  |
| (10) | (172) | 1971 | (With J. Gavin, P. Tippett, P. Teesdale & K. Eldon) Plant agglutinin for another human blood-group. <i>Lancet</i> <b>i</b> , 1130.  |
| (11) | (215) | 1983 | (With R.R. Race) Some early and surprising blood group findings. <i>Vox Sang.</i> <b>44</b> , 126–128.  |

