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*Biogr. Mems Fell. R. Soc.* 2016 62, 461-481, published 1 June 2016 originally published online June 1, 2016

Supplementary data

"Data Supplement"
http://rsbm.royalsocietypublishing.org/content/suppl/2016/05/23/rsbm.2016.0003.DC1

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Elected FRS 1973

BY F. GIANNELLI* FRCP

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Paul Emanuel Polani: an indefatigable man of medium height and athletic constitution, with piercing brown eyes and warm, gentle manners; a sharp, deeply cultured intellect with an unquenchable desire to learn; a mind always seeking deeper understanding through study, observation and correlation; a person of deep controlled emotions, lasting affections, strong morals, and profound respect for his fellow human beings; a life affected by the troubled Italian politics of the 1920s and 1930s, and forced by war to delay dreams of genetic research and to show instead great medical and surgical prowess. In his late thirties Paul Polani began to fulfil his research dreams. He realized that, contrary to expectations, sex determination in humans did not follow the Drosophila-based model, because humans with an XO sex chromosome complement are female, while those with a Y chromosome are male even when they have two X chromosomes. He also discovered that Down syndrome is sometimes caused by chromosomal translocations that, if inherited from unaffected carriers, may cause familial clustering of the disease. This was the first stimulus to the development of prenatal chromosomal tests. Then in 1960 he established a multidisciplinary unit at Guy’s Hospital, London, to investigate diseases of mainly genetic aetiology, and apply research findings to clinical care, while adhering to clear ethical principles. In doing so he demonstrated originality, breadth of vision, and inspiring leadership, and is rightly considered one of the most influential founders of modern medical genetics.

FAMILY, EDUCATION AND EMIGRATION

Paul was born on 1 January 1914 in Trieste, then part of the Austro-Hungarian Empire. His father, Enrico, had been born in Bohemia in 1883, attended business school in Vienna, and moved to Trieste, where he became Head of Forwarding at the Compagnia Adriatica.
His mother, Elisabetta (Elsa) Zennaro, born in Trieste in 1889, graduated from the Scuola Commerciale and became a secretary at the Compagnia Adriatica, where she met Enrico and married him in 1912. From the summer of 1914 Enrico served in the Austro-Hungarian army as an infantry officer on the Serbian front, and then as a garrison officer in Ototac (now in Croatia). At the end of World War I he returned to Trieste, which had become part of Italy, and Paul’s younger brother, Renato (Ray), was born there in 1923.

Enrico and Elsa complemented each other perfectly, providing a rich education for their children. Enrico, scrupulously honest and hard-working, instilled discipline by example, and deeper values through love, logic, equanimity, consistency and dialogue. Elsa, highly intelligent and perceptive, was a patient dedicated teacher with an infectious thirst for knowledge. She taught herself French, German, mathematics and music, and enjoyed playing the piano. Paul felt that he and his family had been very fortunate in having her as wife and mother, since she was a paragon of sensibility, gentleness and caring love. Enrico was not religious, but Elsa was Catholic, and their children were raised with strong Christian values. Paul described his religious beliefs as simple and primitive, with an intuitive faith in a personal God.

Paul’s parents were liberal social democrats, and Elsa strongly supported female emancipation. Both Paul and Renato were raised in this political spirit. Postwar depression, political change and diminished trading activity in Trieste combined to thwart Enrico’s efforts to improve his family’s standard of living by establishing his own forwarding agency.

Paul, during his secondary education at the Liceo Classico Francesco Petrarca, achieved marks high enough to exempt him from school fees. He enjoyed all subjects, but especially the arts; biology had to be supplemented by private reading, and it was then that Paul became intrigued by genetics, which had the allure of mystery and the prospect of new discoveries.

Paul’s leisure was occupied by riding and sailing. His closest school friend was Gaetano (Tano) Kanizsa, with whom he shared ideas, principles and an enthusiasm for learning. Their interests were reciprocally stimulating: Tano was interested in neuropsychiatry and psychology and, later, Gestaltism, whereas Paul was interested in medicine and genetics. They spent hours discussing and trying to fathom out obscure concepts in their respective fields of interest, sometimes moonlighting to attend to their extracurricular activities undisturbed. Paul lost track of Tano during the war and was told that he had died. However, many years later, while reading Francis Crick’s *The astonishing hypothesis*, Paul had the joy of seeing Tano’s name mentioned in relation to Gestalt psychology: he, too, had survived the war and made his professional mark!

In 1932 Paul graduated from the Liceo Francesco Petrarca with excellent marks, and applied to the universities of Padua and Siena to study medicine. Both universities offered him scholarships, but Paul chose Siena, where the ratio of students to academics was a favourable 6:1. Most senior teachers had high academic standards, and for ambitious younger teachers Siena was a stepping-stone demanding industry and commitment to teaching and research. Medicine apart, Siena offered admirable artistic opportunities, including concerts at the famous Accademia Chigiana.

Teaching at Siena was excellent, and students were encouraged to assist with research. In his first year Paul became an intern in biology with Professor Umberto D’Ancona, and chose genetics as his special topic. D’Ancona’s department was well run, with opportunities for practical work and a very good reference library including classics in Italian, German, French and English. Paul was excited by the genetics course, which included discussions of Thomas
Hunt Morgan’s work on *Drosophila*, and frequent reference to the ‘gold standard’ text by Edward Beecher Wilson. Furthermore, D’Ancona was convinced that humans would occupy a central place in genetics, and in support of this view he often quoted British scientists.

In his second year, Paul came into closer contact with medicine, and found the courses admirable, enjoyable and exciting. He became an intern in anatomy and, in his third year, a dissection room demonstrator. With Dr Fausto Sistini, Paul also worked on the distribution of the abdominal sympathetic fibres in the frog, using microdissection of fibres selectively stained with quinacrine, under ultraviolet, and published his findings.

Paul next applied for a three-year internship in the Department of Physiology. However, in 1935 he gained a place, won in open competition, at the National Medical College of the Scuola Normale Superiore di Pisa, an institution of the highest standing and stringently selective. Fortunately, the Professor of Physiology in Siena, Igino Spadolini, also moved to Pisa, and Paul continued his physiology internship under his guidance. He graduated in medicine in 1938, with an honours MD and a thesis entitled ‘The humoral transmission of the nervous impulse and the distribution of cholinesterase’. Then, after a year of rotating internship in Trieste General Hospital, he obtained the state qualification to practise medicine.

At that time membership of the Fascist Party was essential for employment, and for this reason Paul left Italy. On 1 August 1939 he arrived in Guernsey to stay with friends, and a month later he travelled to London and registered with the General Medical Council, which had a reciprocity agreement with Italy.

**Effects of World War II on Paul’s Life and Career**

**Career**

Paul intended to follow a postgraduate crash course at Hammersmith Hospital, but the start of the war put an end to this idea. A few lean and spartan months followed. Nights as a dishwasher at Kettner’s in Soho provided some income, and days spent reading in the British Medical Association’s library provided knowledge, warmth and comfort. As learning English was essential, watching films (two performances at a time for the price of one) was an obligation, not a luxury.

Towards the end of 1939 Paul enrolled as a Surgeon Lieutenant on SS *Adrastus*, bound for the Far East. She was a naval auxiliary on convoy duty and had the Convoy Commodore on board; the skipper, Captain Lesley, was an ex-RN Cornishman. Paul, well accepted and only gently teased by the crew, had several sick or injured sailors to attend to.

During the return journey from the Far East, Italy entered the war. Captain Lesley called Paul to his cabin and told him that from that moment he had to be considered an enemy alien; he then poured two glasses of sherry and proposed a toast to their friendship.

On arrival home Paul was met by the police and interned with other Italians, first at Lingfield Racecourse, and then in a former cotton mill in Bury St Edmunds. From there he was supposed to sail for Canada in SS *Arandora Star* but, at the last minute, a Maltese intelligence officer sent him to the Isle of Man where a doctor was needed in an internment camp. This saved Paul’s life, as the *Arandora Star* was sunk by the Germans.

Paul helped to set up a hospital at Grenville Camp in Douglas, which turned out to be quite busy (see Chappell 1984). He remained there until March 1941, when he passed the scrutiny...
of the Camp Tribunal and was released to go to London, where doctors were needed. The Emergency Medical Service was organizing a research appointment with Professor Owen de Wesselow, to work on crush injuries and wound shock, when Paul was asked to do a stint as locum at the Evelina Hospital for Sick Children in Southwark. As the post holder did not return, Paul was appointed Resident Medical and Surgical Officer, in charge of the borough’s first aid post.

Until 1946/47 Paul remained the only Resident at the Evelina, but a part-time outpatients officer was found to help with outpatients and on the wards. Two consultant paediatricians did weekly outpatient clinics and consultations on the wards. The only consultant general surgeon was the senior surgical registrar at Guy’s (Sam Wass), a busy man indeed. He and the two paediatric specialists were on call, but most of the clinical and surgical work was left in the hands of junior doctors, helped by the extremely able and knowledgeable sisters.

Students from Guy’s hospital came to clerk and be taught at the Evelina Hospital, because the children’s wards at Guy’s had been closed. Thus Paul had the stimulus and satisfaction of teaching at the bedside.

When the consultants returned from wartime service, and hospitals were resuming their normal working pattern, Paul felt it was time to go. For some years he had had day-to-day responsibility for more than 100 children requiring medical or surgical attention, and had performed some 1500 surgical operations. He had found the work incredibly satisfying and rewarding, sobering, and conducive to maturation and thought. Administrators had been supportive and friendly and he noted, in a personal communication to me, that the courageous, uncomplaining, adaptable, humorous, jolly and unimaginably kind people of Southwark had accepted him without ever asking why he was there. He was clearly an oddity but, he was there with them and they had given him a new home and indelible memories to treasure in his heart.

These feelings were obviously reciprocated. Some 15 years later I discovered some fruit-sellers near London Bridge station who remembered Paul tending to them as children. They proudly showed me the fading marks of his surgical work, and adopted me as their friend, on his account. My family doctor, who had trained at Guy’s during the war, also remembered Paul, whom he defined as a human dynamo with inspirational teaching ability.

Family

In 1942 Paul met Nina Sullam, and they married in 1944. Nina was born in Poland in 1921, the only daughter of an Ottoman diplomat and Juliette Rossolato, of French origin but born in Istanbul. Nina attended junior school in Trieste, and then the Milan Conservatorio, where she obtained a concert pianist diploma. In 1938, after moving to London with her family, Nina abandoned her musical career for secretarial work in the Italian Section of the BBC European Services, which she left in 1962 to train in biology and statistics.

Nina had charm and character, and proved able to do whatever she set her mind to. Paul described her as an admirable companion and colleague: loyal, intelligent, alert, willing, active, able, tireless, highly motivated and modest. Paul and Nina shared a passion for horse-riding. They bred and broke a thoroughbred, which learned to utter three phonemes: one for Paul, one for Nina and one for horses. Skiing was Paul and Nina’s holiday passion, with music and reading their other hobbies (Paul read poems in five European languages, and a few in ancient Greek and Latin). Nina and Paul had no children, but they shared every aspect of life in intense and perfect harmony.
The war interrupted Paul’s contact with his family in Trieste, to his great regret. Paul’s father died on 14 March 1945, but Paul could not be at his bedside. On 25 July 1944 Paul’s brother Renato joined the partisan Brigata Garibaldi ‘Fratelli Fontanot’ to fight the Germans in the mountains of Slovenia, returning to Trieste on 17 May 1945. When Tito occupied Trieste, Renato went to Venice as an Allied court interpreter, returning to Trieste 40 days later, when Tito was evicted by the Allied forces. He then returned to his medical studies at Padua University, but wartime deprivation affected his health. He became seriously ill in 1946 and had to abandon his studies for 18 months of medical treatment, supported by his mother, Elsa, and financially by Paul. When Elsa died in 1962, Paul expressed his pain at this loss of family contact during the long war years.

**RETURN TO RESEARCH AND TO GENETICS**

In 1948 Sam Wass advised Paul to specialize in surgery because he was so gifted, but Paul wished to fulfil his youthful dream of research in genetics. Richard Ellis, consultant paediatrician to Guy’s and the Evelina, and his successor, Philip Evans, supported Paul’s wish to do research. He obtained a two-year National Birthday Trust paediatric research fellowship working on clinical kernicterus (brain damage induced by bile pigment (1)*) and subsequently became assistant to Evans, then the director of the Paediatric Department, with whom Paul and his wife Nina established a lifelong friendship. This job gave Paul time to absorb the theory of human genetics and, from 1950, to begin genetic research under the stimulating influence of the staff of the Galton Laboratory, where he was attached to Professor Lionel Penrose (FRS 1953) as a visitor.

At Guy’s Paul had established good relationships with Peter Bishop, the sex endocrinologist, and Maurice Campbell, the cardiologist. Guy’s Hospital was the Mecca for patients with congenital heart disease, and Paul began a series of studies on the genetics of these defects. At the same time he collected data on Turner syndrome, and females with ovarian agenesis, in collaboration with Peter Bishop’s two registrars (Maurice Lessof and Joe Briggs) and an overseas visitor (Carlos De Almeida).

Guided by Penrose, Paul set about disentangling the influence of maternal and paternal age, and parity, on congenital heart disease, while trying to explore other factors: gender, consanguinity, association with other anomalies, infection and other environmental variables. Penrose followed and advised on this work, and was particularly intrigued by a small but significant effect of paternal age in coarctation of the aorta (a narrowing of the aorta in the region of insertion of the ductus arteriosus). Paul was more intrigued by the observation that coarctation of the aorta was clearly a vascular defect disproportionately affecting males, and yet was very common in females with Turner syndrome and so-called ovarian agenesis (3). He therefore wondered whether these females could have an XO sex chromosome constitution. Penrose, with a natural antipathy to hypotheses based on slim evidence, disliked Paul’s idea, with its implication that sex determination in humans would differ from the *Drosophila* model (in which XO individuals are males and XXY are females). However, working with various collaborators Paul first showed (2) that cells from women with Turner syndrome/ovarian agenesis were sex chromatin negative, like

* Numbers in this form refer to the bibliography at the end of the text.
male cells, thus supporting the XO hypothesis. Second, he demonstrated that these females had a male frequency of colour blindness, whereas males with Klinefelter syndrome, whose cells were sex chromatin positive, had a female frequency of this X-linked defect (4, 5). Thus, genetic data indicated the presence of a single X chromosome in females with ovarian agenesis, and the presence of two X chromosomes in Klinefelter syndrome males. This strongly suggested that in humans sex determination was not based on the ratio of X chromosomes to autosomes, as in Drosophila.

Since 1955, Paul—who had by then become research physician for the National Spastic Society (NSS) and director of their Medical Research Section, based at Guy’s Hospital—had wished to find a direct proof or refutation of his unorthodox views on the sex chromosome constitution of Turner females and Klinefelter males. An attempt with Dr Gordon Thomas did not yield adequate chromosome preparations and, after an unsuccessful approach to Peo Koller, Paul turned to Charles Ford (FRS 1965). He had come to know Ford through the work on sex chromatin and colour blindness, and they had become better acquainted after Paul suggested that Ford should be invited to the 1957 Nuclear Sexing Symposium at King’s College Hospital. Ford’s collaborator John Hamerton was also at the meeting and a collaboration was started to study human anomalies of sex differentiation. In the spring of 1958 Paul received Ford’s preprint of a method for the study of human chromosomes in bone marrow cells, and he immediately sent Ford bone marrow from himself and patients with Turner and Klinefelter syndromes.

At the end of the summer of 1958, at the request of the World Health Organization Regional Office for Europe (WHO/Europe), Paul was seconded by the NSS to work on a large investigation of pregnancy wastage being planned in the USA. The headquarters of WHO/Europe were in Copenhagen, where Paul enjoyed free access to the university library, and the opportunity to discuss sex determination with Mogens Westergaard, who had identified the male-determining role of the Y chromosome in Melandrium and was sympathetic to Paul’s theory of sex determination in humans.

Browsing and re-reading classic human chromosome papers, and especially Ford and Hamerton’s meiotic in vivo confirmation (Ford & Hamerton 1956) of the human chromosome number (23 pairs), Paul recalled Ursula Mittwoch’s paper on a male with Down syndrome whose meiotic chromosome count appeared to be 24 (Mittwoch 1952). He then went on to wonder whether Mittwoch had miscounted, or whether the chromosome number in Down syndrome was abnormal.

Towards the end of 1958 Paul received from Ford the exciting news that the bone marrow from a female patient with Turner syndrome had shown 45 chromosomes, and an XO sex chromosome complement. Furthermore, a male patient with Klinefelter syndrome had been shown to have 47 chromosomes, and an XXY sex chromosome complement, as well as some cells with a 46,XX karyotype; he was thus probably a sex chromosome mosaic. This good news, together with Paul’s reflections on the role of the Y chromosome in sex determination, and on Mittwoch’s Down syndrome paper, required discussion and planning for further action. Accordingly, in January 1959 Paul arranged to meet Ford at Heathrow, en route from Copenhagen to the National Institutes of Health (NIH) in Bethesda. It was decided to publish the findings from the Turner syndrome patient in the Lancet, because this journal had previously shown interest in Turner syndrome (6). The findings in this patient, and in the male with Klinefelter syndrome, clearly indicated that the Y chromosome acted as a male factor, and that sex determination in humans therefore differed from that
in *Drosophila*, as Paul had earlier proposed. The patient with Klinefelter syndrome also appeared to be a mosaic, and *Nature* seemed the appropriate journal for these findings (7). Ford was also to report these matters at the forthcoming meeting of the Medical Research Society. In addition, Paul and Ford needed to investigate the chromosomes of patients with Down syndrome as a matter of urgency, because they felt that trisomy of a small chromosome was feasible. Paul, aware of Penrose’s observations on the maternal age effect in Down syndrome, was particularly interested in patients born to young mothers, not only because they represented an exception to the common rule but also because some young mothers had more than one child with Down syndrome. However, as these patients were rare, their investigation was postponed to a later time. Paul then continued his journey to Bethesda.

At the NIH Paul, acting as a consultant/observer for WHO/Europe, was attached to the National Institute of Neurological Disease and Blindness, directed by Richard L. Masland, who also directed the Pregnancy Wastage Collaborative Study on which Paul was to work. This sought to identify factors responsible for abnormal development, leading to mental, neurological and physical abnormalities. The prospective study was to start by enlisting 40000 newly pregnant women and their subsequent offspring. Each woman was to be monitored throughout pregnancy in 14 university hospitals, using detailed, standardized, clinical and biological investigations, and their offspring were to be studied in a comparable manner at delivery, and again later if they survived. Paul’s task was to determine whether it seemed desirable and feasible to undertake parallel work in the UK, Eire and Scandinavia.

As soon as Paul arrived at Bethesda, Ford rang him to report that Jerome Lejeune had found that patients with Down syndrome had 47 chromosomes and were trisomic for a small acrocentric chromosome, later called no. 21.

It was likely that Lejeune *et al.* (1959) had examined patients born to old mothers, as they were the most common. Paul and Ford therefore went on to examine patients with Down syndrome born to young mothers. In this way they identified ‘Down syndrome with 46 chromosomes’, because the trisomy was ‘hidden’ by the centric fusion of chromosome 21 with a larger acrocentric, resulting in a single abnormal submetacentric chromosome (8). This abnormality was transmissible through asymptomatic translocation carriers, with a chromosome count of 45 (9). Paul reported this at the December meeting of the American Neurological Society.

It was for this work, and particularly that on Turner and Klinefelter syndrome, with their bearing on sex determination in humans, that, 14 years later, Paul was elected a Fellow of the Royal Society.

**Foundation of the Paediatric Research Unit**

Paul’s work for WHO in Europe and the USA necessitated frequent transatlantic crossing, and attendance at planning and standardization meetings. This allowed him to get a clear idea of the American academic set-up, and he was able to meet American groups interested in the development of cytogenetics and other aspects of human genetics. Furthermore, when Paul presented his work on sex chromosome abnormalities and sex determination in humans to an audience of specialists meeting in Syracuse in the summer of 1959 (10), at the invitation of Lytt Gardner, he had the opportunity to meet such people as Francis Crick FRS, Barton Childs.
and James Neel, and also William Russell, who presented work on the mouse that paralleled Paul’s work in humans. For Paul it was a rich time for discussions that helped the development of his thoughts on research.

In 1960 Paul reported to WHO/Europe on his observations in the USA and on his consultations in the UK, Eire and Scandinavia. It was agreed that the American study would be critically important to a variety of matters relating to pregnancy and its outcome. However, it was thought that a similar European study was not feasible because the intricacies of the work and the need to build the necessary facilities and to ensure standardization required an impracticable level of investment and commitment. Nevertheless, it seemed useful to duplicate specific parts of the project in those European Units where these issues were under active consideration.

In the UK, the NSS, under the influence of its progressive director and Medical Advisory Council (MAC), had begun to consider a strategy for future research into prevention in 1959. At the suggestion of the MAC, the NSS had set up a Research Advisory Council (RAC), chaired by Sir Alan Moncrieff. Its members were Professor G. Daniel (neuropathology), Dr Ronnie MacKeith (paediatric neurology), Professor Lionel Penrose (genetics), Dr P. Phillips (neurophysiology) and Sir Charles Symons (neurology), together with senior members of the NSS executive and members of the MAC.

The RAC agreed that research should focus on primary prevention. They considered two aspects: first, that research should be comprehensive and cognizant of the variety of neurodevelopmental disorders that manifest as neurological diseases, learning disability or cognitive, emotional or sensory dysfunction; and second, that research should be fundamental and basic, considering development generally (including the origin of malignancy), and more specifically developmental neurobiology. Paul suggested that an integral aim should be the immediate practical application of research findings for the benefit of patients through diagnosis, counselling and prevention.

The RAC considered that this programme could be implemented by supporting different facets of research in different centres—each concerned with a different disorder—or by establishing and supporting a single dedicated centre capable of developing the required comprehensive approach. The latter option would allow easier integration of approaches, technical facilities and methods, together with more purposeful and direct translation of research findings into clinical practice. The need for expertise in different areas would be met by multidisciplinary staffing.

At the end of his secondment to WHO/Europe, Paul reported his observations on the Pregnancy Wastage Collaborative Study and on his concurrent genetic research, to both MAC and RAC. After this, the chairman of the NSS asked him to prepare a blueprint for a comprehensive, unitary approach that would meet the objectives and research principles set out by the RAC. Paul did so, stipulating that the proposed multidisciplinary unit should have a genetic leitmotif. His plan was accepted and on 1 October 1960 the Paediatric Research Unit (PRU), an academic unit based at Guy’s Hospital, was founded. Paul, appointed by the University of London as the first Prince Philip Professor of Paediatric Research at Guy’s Hospital Medical School, became the director of the Unit, geneticist to Guy’s Hospital and Medical School, and honorary paediatrician to the hospital (figure 1).
Paul Emanuel Polani

Initial structure of the PRU

Paul’s idea of a multidisciplinary research unit with a genetic philosophy and a structure suited to the rapid translation of research findings into clinical practice was original. That the NSS accepted its format and aims was a reflection of the esteem that Paul had garnered during his association with the Society. The Unit itself bore witness to Paul’s ability to guide and inspire through example, commitment and fellowship. It also adapted rapidly to changes in its field of research, thus demonstrating both the validity of Paul’s research philosophy and his ability to nurture wide-ranging research interests. In essence the PRU was the embodiment of Paul’s boldness and foresight, and it illustrated his belief that medical genetics was not merely that branch of medicine caring for families affected by diseases with a mainly genetic aetiology, but it must also include the multidisciplinary research necessary to understand such diseases, and the rapid and ethical translation of research findings into clinical care. Because he realized this vision, Paul has been recognized as a founder of the modern field of medical genetics, and the individual who did more than almost anyone else to influence the development of medical genetics, particularly in Europe (Harper 2007).

The NSS made a generous endowment of £2 million, spread over a period of 10 years, to cover (i) interim accommodation, (ii) the conversion of the Down warehouse into research premises (Cameron House), (iii) the progressive establishment of senior university research posts, (iv) the employment of ancillary graduates, technical and administrative staff, (v) library services, an animal station, photography, administration and secretarial assistance, (vi) the initial and provisional running of research projects, (vii) uncommitted funds for.
pump-priming of new research projects and strategic developments, and (viii) contributions to new laboratories and to the children’s wards in Guy’s Tower.

At the outset John Hamerton was appointed Senior Lecturer and head of the Cytogenetics section, and with him Paul planned the restructuring of the Down warehouse, which was completed in 1962. Until then Cytogenetics, a ‘Clinical’ group and an ‘Epidemiology and Statistics’ group (related to Paul’s previous position as director of the NSS Medical Research Unit) were housed in temporary accommodation.

In 1961 the PRU established an Experimental Biology section, with Roy Spector as Senior Lecturer, and in 1962 a genetic service, dealing mostly with regional referrals. The Biochemistry section, with Philip Benson as Senior Lecturer, followed in 1963. In 1964, after his retirement, John Fraser Roberts FRS joined the Unit as consultant geneticist, and in 1965 the Developmental Immunology section, with Matteo Adinolfi as Senior Lecturer, completed the Unit’s research structure.

Paul ensured that each part of the Unit worked smoothly and that the different parts worked well together. He offered encouragement, advice, ideas and help to optimize efficiency. His directing skill was based on warmth, cheerful empathy, generous modesty and the ability to enjoy people’s successes more than they did themselves.

Paul’s own research focused principally on Down syndrome and on the sex chromosome abnormalities associated with anomalies of sex. In 1961 the first evidence was obtained that, in Down syndrome families, the rate of transmission of translocations involving chromosome 21 and a large acrocentric chromosome (a D/G21 translocation, in 1960s terminology) was lower from male than from female carriers (11). After the accumulation of a large amount of data, the first estimate of the population frequency of Down syndrome due to translocations involving chromosome 21 (that is, D/G21 and G21/G in 1960s terminology) was obtained, and Paul calculated the mutation rates for these translocations (14). This was the first estimate of the rate at which centric fusions between acrocentric chromosomes occurred in a human population. For the families of translocation Down syndrome individuals, prenatal diagnosis was essential. Paul strongly encouraged the development of appropriate methods, and the first prenatal diagnoses for chromosomal disorders were undertaken in 1969, shortly after the UK abortion laws allowed.

Paul’s analysis of phenotypic variation among patients with Down syndrome indicated that somatic mosaicism, resulting in patients with a significant proportion of cells with a normal karyotype, was associated with a milder phenotype (13). This induced him to develop an experimental system to explore the possible curative effects of transplanting normal cells. In collaboration with Dr Mary Seller of the Experimental Biology section, cells from normal mice were transplanted into mice with a congenital anaemia, which cured their anaemia (16). Paul and his wife, Nina, also examined the dermatoglyphics of mosaic individuals with Down syndrome, to investigate the subtler effects of mosaicism (17).

Paul also examined a large number of women with abnormalities of sexual development. This helped, first, to assign the genes for the Xg blood group, which were known to escape X chromosome inactivation, to the short arm of the X chromosome (12) and then to show that these genes did not escape inactivation when they were on structurally abnormal X chromosomes (19).

Paul’s clinical expertise was much sought after by his colleagues at Guy’s Hospital, and one of these interactions led to the identification of a new syndrome of cardiomyopathy and lentiginosis (15, 20).
Paul was, and remained, in high demand as a writer of reviews, and he dealt with these rigorously and with insight. For example, while reviewing autosomal abnormalities, he noted the frequent occurrence of retinoblastoma in patients with deletions in the long arm of a D chromosome (18), thus highlighting data relevant to the position of the ‘retinoblastoma’ gene. In a review on pairing of the X and Y chromosomes, he brought a variety of data to bear on the location of the ‘maleness’ gene on the Y chromosome, and on the role played by illegitimate unequal crossing-over between the X and Y chromosome short arms in causing discrepancies of sex determination (31).

**EVOLUTION OF THE PRU**

By the 1970s the PRU was ready for further expansion. The discovery by Caspersson et al. (1968), that fluorescent staining methods allowed precise chromosome identification and detailed analysis, permitted the extension of cytogenetic diagnosis to subchromosomal levels, and hence its application to a new range of disorders. This required the recruitment of new staff both in the laboratory and in the clinic. The development of cell fusion and hybridization also opened new research fields. From this point onwards, funding for the Unit’s research activities was essentially based on grants from national research-supporting bodies.

In 1971 John Hamerton left to take up the Chair of Genetics at the University of Manitoba, and Michael Daker was appointed Lecturer in charge of cytogenetic diagnoses, and Mary McGuire, whom John Hamerton had recruited as a tissue culturist, became chief technician in charge of tissue culture services. Paul also inspired and supported a systematic cytogenetic study of spontaneous abortion (overseen by Eva Alberman), to determine the contribution of different chromosomal abnormalities to the aetiology of early pregnancy loss (Creasy et al. 1976).

I had the task of establishing a cell biology research group; this required additional tissue culture facilities, which were funded by a private donation to Paul. I decided to investigate diseases manifesting abnormal sensitivity to DNA-damaging agents, and predisposition to cancer. Paul was interested in some of these diseases, particularly Bloom syndrome (23, 26), and he encouraged the development of prenatal testing for families with these disorders (see, for example, Ramsay et al. 1974; Giannelli et al. 1982).

In 1971 the diagnostic work of the Unit was partly funded by the National Health Service (NHS). Diagnostic activity expanded further in 1972, with the development of prenatal tests for neural tube defects, based on increased levels of α-fetoprotein in amniotic fluid (Seller et al. 1973). Paul also encouraged Mary Seller’s participation in the exploration of the importance of environmental and nutritional factors in the aetiology of neural tube defects. This collaborative venture identified maternal vitamin status, and in particular folic acid deficiency, as the principal causative factors, and led to the effective prevention of neural tube defects (Smithells et al. 1980). Mouse models were also used for in-depth studies of neural tube development and its abnormalities (27).

In 1973 the Supra-Regional Laboratory for Genetic Enzyme Defects was established within the Biochemistry section, with Anthony Fensom as Principal Scientist and Lecturer, and by 1974 some of the metabolic defects investigated could be detected prenatally (22). In 1974 Caroline Berry joined the Unit. She became a consultant clinical geneticist in 1979 and remained the Unit’s senior clinical geneticist until her retirement in 1997. In 1975 the PRU moved to floors 7 and 8 of Guy’s Tower and various services were expanded.
In 1976 the South-East Thames Regional Genetic Centre, fully supported by the NHS, was established within the PRU. In 1979 Paul and his colleagues published a review of the genetic service that had been provided by the PRU over the previous 16 years (28). Paul also helped to establish a centralized facility for automated cell and chromosome sorting, used by Matteo Adinolfi to investigate whether fetal cells in the maternal circulation might allow non-invasive prenatal diagnostic tests (Adinolfi 1982).

In the late 1970s molecular genetics burst onto the scene, leading Paul to try to introduce this ‘new genetics’ to the PRU, through meetings involving interested London groups. However, he soon realized that deeper involvement was necessary. New funds were needed both to enter this field and to provide for the future of the PRU. In 1976 a fund-raiser was appointed, but proved insufficient to our needs. Accordingly, in 1978 Paul tried fund-raising through the medium of personally motivated individuals with a wide range of useful contacts. On the advice of the director of the NSS (Tim Yeo), the Generation Trust was set up. Through Yeo’s contacts Paul attracted Philip (later Lord) Harris, who quickly organized a group of influential trustees. These were joined by Nils Taube, whom Paul had met by mere coincidence when they shared the same flight. Under the patronage of Prince Philip, it was hoped that the Trust would soon be in a position to contribute substantial funds. At this point, Paul asked whether I would like to take a sabbatical year in a molecular biology laboratory, and then establish a PRU Molecular Genetics section.

I was lucky enough to be able to spend this sabbatical at the laboratory of George Brownlee (FRS 1987) in the Sir William Dunn School of Pathology at Oxford University. It was 1982, and I was assigned to a fast-moving project that enabled me to learn a variety of techniques, meet several able young scientists, and learn about the work of John (now Sir John) Sulston (FRS 1986) on the genome of *Caenorhabditis elegans*.

On my return to London a molecular genetics laboratory was soon established (figure 2), initially with a small donation from the Medical School and a research grant. Then the work expanded and, when funds from the Generation Trust became available, we were able to buy essential equipment and appoint a senior scientist, Dr David Bentley, whom I had met during my sabbatical. In short order we developed rapid methods of mutation detection (Montandon *et al.* 1989; Rowley *et al.* 1995), implemented a national strategy to optimize genetic counselling for families with diseases characterized by high mutational heterogeneity, for example for patients with haemophilia B (Giannelli *et al.* 1992), and developed and applied procedures necessary for the construction of cloned maps of human chromosomes (see, for example, Bentley *et al.* 1992; Holland *et al.* 1993).

By this time Paul had officially retired, but he continued to come in daily to the PRU, to pursue his personal research with his very talented assistant John Crolla, attend the Generation Trust meetings and watch over the health and continued growth of the Unit he had created and nurtured for so many years. He continued to offer advice in the fields of genetics and paediatrics, both nationally and internationally, well into the 1990s. He was invited to deliver named lectures until 1996 and to contribute keynote addresses to genetic meetings until 2005. His successors as directors of the Unit were Professor Martin Bobrow (1983–94; FRS 2004) and Professor Ellen Solomon (1995–2008).
Research on meiosis and Paul’s last life challenges

In 1969 Paul took a sabbatical to study meiosis, a focus of his personal research and a passion he shared with Georgiana Jagiello, a frequent visitor to the PRU, who later became Professor of Human Development and Genetics at Columbia University.

Paul compared the behaviour of chiasmata and centromeres in male and female murine meiosis (21) and used electron microscopy to examine the pairing and segregation of Robertsonian translocations in trisomic mice (32, 33). In infertile men, he demonstrated the contribution of meiotic chromosome abnormalities to their infertility (24). With Georgiana Jagiello, Paul made a first attempt (25) at testing the production line hypothesis of Henderson & Edwards (1968) in mice: this suggested that a decrease in the number of chiasmata in the oocytes, as the age at conception increased, might explain the maternal age effect in aneuploidy. The results appeared partly to support this proposition. Then Paul, with the help of Mary Seller and John Crolla, devised a second experiment in mice to test the basic idea that the first oocytes that mature in the embryo are also the first to be released from the ovary after puberty, whereas the converse is true of later-maturing ova. This test required the development of a technique involving ovary explantation, in vitro maintenance, and reimplantation in spayed females, so that fetal oocytes could be radioactively labelled at different times in vitro and then harvested at different times after puberty and maturation in vivo (29). The results that Paul obtained supported the production line hypothesis in mouse oogenesis (34). This in vitro/in vivo method of
oocyte analysis was also developed to observe meiotically paired chromosomes, each with sister chromatids differentially labelled with bromodeoxyuridine, to study what happens at chiasmata (30). This was an important step in unravelling the complex story of chromosome recombination through breakage and reunion, and its relation to chiasmata and their possible terminalization.

Seeing Paul, after his retirement in 1982, coming into his laboratory every day was a joy for all his old staff. His agile, energetic step, his warm smile and his youthful, piercing eyes seemed to tell us that time was passing much more slowly than it really was. Then, late in 1989, he unexpectedly stopped coming. We were sad and wondered what might have happened, but Paul was certainly entitled to a peaceful retirement and we respected his privacy. Obviously he was well and active, because he was making intense use of the Unit library services, publishing papers and filling national and international advisory roles. I rang him from time to time. Paul liked to receive copies of our papers, and also photocopies of any interesting publications we came across. In the early 1990s, when his wife, Nina, answered the phone, she seemed reluctant to converse, and frequently failed to pass messages to Paul; I wondered whether she considered phone calls a bit of an intrusion. Then, in the spring of 1998, Paul wrote me a letter saying that in 1987 Nina had begun to show signs of a progressive neurological degenerative disease, which was now seriously advanced. His letter detailed Nina’s current needs and listed useful addresses so that she could receive the best possible care if he suddenly became unable to provide it. I thought then that Paul’s sudden disappearance from the Unit was explained by the need to look after Nina. Sadly her decline worsened, and she died at home on 29 December 1999.

In the new millennium Paul returned to the Unit (figure 3); he visited new members of staff to hear about their research, regularly attended the annual Unit Research Days when Unit members communicated their results, and always contributed to the discussion. He spent many days in the library of the Royal Society of Medicine, and published papers until 2004. He went to Trieste and Udine frequently, and spoke at length to his brother Renato and his only niece (Julia Polani Ause), in Oregon, on a daily basis.

In the summer of 2005 Paul was invited to chair a medical genetics meeting in Italy. He left full of enthusiasm, as he planned to revisit places he had loved in his youth. However, on his (delayed) return, I learned that an acute illness had frustrated his plans. His voice was as firm as ever, and his health had apparently recovered. I rang him before Christmas, to convey seasonal good wishes and to arrange a visit after my return from Christmas with my family. On my return I rang him repeatedly, but without an answer, and Matteo Adinolfi also failed to contact him. From a neighbour we learned that Paul was in hospital—he had not told us that his illness in the summer had been acute leukaemia. He seemed stable, and was receiving treatment when I went to visit him. I expected to see some scientific journals in his room, but there were none. When I asked him what he was reading, he told me that he had the writings of St John the Evangelist and St Paul.

In early February Paul’s brother, Renato, who had flown over from Portland with his wife, Anita, rang to say that Paul’s treatment had been unsuccessful, and that he wished to say goodbye. For the first time he looked frail. He asked me about the Unit, and when I told him that it was going from strength to strength he smiled. We had a warm goodbye, and a few days later, on 18 February 2006, Paul died.
Honours

1961 Fellow of the Royal College of Physicians, London
1973 Fellow of the Royal Society
1979 Fellow ad eundem of the Royal College of Obstetricians and Gynaecologists
1980 Emeritus Professor of Paediatric Research, University of London
Honorary Fellow of the Associazione di Genetica Italiana
1981 Commendatore of the Order of Merit, Republic of Italy
1982 President of the Association of Clinical Cytogeneticists of Great Britain
1984 Honorary Member of the British Paediatric Association for outstanding contribution to Paediatrics
Honorary Fellow of the Royal College of Pathologists
1985 Senior Member of the Association of British Neurology
1989 Honorary Fellow of the Royal College of Physicians of Ireland
1994 Honorary Fellow of Guy’s and St Thomas’ Hospitals Medical Schools
1995 Life Member of the British Medical Association
1997 Honorary Fellow of the Royal College of Paediatrics and Child Health
1998 Fellow of King’s College, London
1999 Honorary Fellow of the Società Italiana di Genetica Umana
Awards

1974  Kenneth Craik Research Award, University of Cambridge
1984  Sanremo International Award and Prize for Genetic Research
1985  Baly Medal of the Royal College of Physicians for distinguished genetic research
1986  Gold Medal of the International Cerebral Palsy Society for genetic and cerebral palsy research
1994  Gold Florin of Florence
2005  Gold Medal of the Universities of Modena and Reggio Emilia, Italy, for contribution to Genetic Research

Named lectures

1961  The Harveian Society of London Lecture
1965  The Bartholomew Mosse Lecture, Rotunda Hospital, Dublin
       The Scientific Basis of Medicine Annual Review Lecture, British Postgraduate Medical Federation, London
       The Woodhull Lecture, Royal Institution of Great Britain, London
1969  The Fundación Jiménez Díaz Lecture, Madrid
       The Mental Health Foundation Lecture, London
1974  The Kenneth Craik Lecture, University of Cambridge
1976  The Harveian Society of London Lecture
       The European Society of Paediatric Research Lecture, Rotterdam
1978  The Scientific Basis of Medicine Annual Review Lecture, British Postgraduate Medical Federation, London
       The George Frederic Still Lecture, British Paediatric Association, York
1979  The Holme Lecture, University College Hospital Medical School, University of London
1980  The Fison Memorial Lecture, Guy’s Hospital Medical School, University of London
1981  The Blake Marsh Memorial Lecture, Royal College of Psychiatrists, London
1982  The Linnean Society Lecture, London
       The Messtitz Memorial Lecture, Sussex Postgraduate Centre
1983  The Ronnie MacKeith Memorial Lecture, Association of British Paediatric Neurologists, Oxford
       The Fison Memorial Lecture, Guy’s Hospital Medical School, University of London
1988  The Harveian Oration, Royal College of Physicians, London
1994  Key address, International Congress of Human Genetics
1996  The Carter Lecture, British Society for Human Genetics, York
2005  Keynote Address, International Symposium on Prenatal Diagnosis, Modena
ACKNOWLEDGEMENTS

This memoir, based on 46 years of association and friendship and on notes by Paul, has been enriched by contributions from Renato Polani, Julia Polani Ause and my colleagues Dr John Crolla and Professor Mary J. Seller. I am greatly indebted to Miss Elizabeth Manners, formerly research secretary to Paul, for contributing to this memoir in many ways including the careful editing of the manuscript, the compilation of the full list of Paul’s publications and the preparation of the figures.

The frontispiece photograph was taken in 1976 by Godfrey Argent and is reproduced with permission.

AUTHOR PROFILE

Francesco Giannelli

In 1958 I obtained an MD degree *cum maxima laude* from Rome University. During the preparation of my thesis I had become aware of Paul Polani’s work on the aetiology of congenital heart disease. I first met him in 1959, when the Medical Faculty of Rome University invited him to give a lecture on his research on human chromosome abnormalities. At the end of the lecture I approached him and asked whether I could spend some time in his laboratory. Paul replied that if I succeeded in obtaining a travelling scholarship I should let him know. I made a successful application to the Consiglio Nazionale delle Ricerche (CNR) and accordingly, on 1 October 1960, I began a placement in the newly established Paediatric Research Unit (PRU), at Guy’s Hospital. Four months later, when my CNR funding came to an end, I was offered a six-month scholarship funded by the PRU, and then a two-year research fellowship. This was the start of 46 happy years working in and for the PRU, comprising 10 years in Cytogenetics, 12 in Cell Biology and 24 in Molecular Genetics. Throughout this period Paul Polani was my mentor and my friend.

REFERENCES TO OTHER AUTHORS


**BIBLIOGRAPHY**

The following publications are those referred to directly in the text. A full bibliography is available as electronic supplementary material at http://dx.doi.org/10.1098/rsbm.2016.0003 or via http://rsbm.royalsocietypublishing.org.


