Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

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Lionel Sharples Penrose, 1898–1972: A Personal Memoir in Celebration of the Centenary of His Birth

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IT is Friday, mid-morning. You are about to leave the city for a long weekend in the country when you find yourself opening your front door to four bedraggled political refugees. It is difficult for you even to recognize the weary man, woman, and two girls as people whose casual acquaintance you had made on a single previous occasion about 2 months ago, during a brief 3-day work-related visit to their country. You invite them in, show them around and, 15 minutes later, the dazed visitors, now ensconced in your home, are waving good-bye to you as you leave for your weekend in the country.

How many people are there among us who would be willing to entrust their homes, in their absence, to practically complete strangers arriving on their doorstep from a foreign country?

Penrose, the man: That morning in late August 1968, in answer to my telephone call intended merely to inform them that we had escaped from our country, which had been invaded by Soviet forces, Lionel and Margaret Penrose invited my husband, daughters, and me for what we thought would be a polite cup of tea. They met us at the door and, to our amazement, instead of a handshake they handed us their house keys, their only set; characteristically, the spare keys were nowhere to be found. Before they drove off waving breezily, and before we realized what was happening, Margaret managed to show me how to prevent the hot water system from exploding and the contents of the linen closet from toppling over and to give me instructions for Mrs. Lee, the cleaning lady, who was apparently expected to arrive at the house at the beginning of the week. Lionel rather nonchalantly provided my husband with what he called "a few useful telephone numbers"! Subsequently, we found that they enabled us to apply for permission to stay in Britain and to obtain work permits and alien cards. The children were given books and within 5 minutes were engrossed in some of Lionel's handmade wooden puzzles.

We had met Professor Lionel (Figure 1) and Dr. Margaret Penrose for the first time during a brief working weekend in Brno, Czechoslovakia, the city where Mendel had made his discoveries. The Prof, as we later affectionately learned to call him, gave some talks; we showed him Mendel's monastery and museum, his garden, archives, and documents; and one evening we took them to the opera. That, at the time of our arrival in London, was the extent of our acquaintance with the Penrose family.

In spite of the season (it was August) Lionel and Margaret were both wearing overcoats when they met us at the door. During the three months we lived at 1 Rodborough Road in Golders Green (north London), we found that they frequently wore thick coats in the house to keep warm. It was not until after the Professor's death in 1972 that the large family house was converted into flats and central heating was installed. Thus, it was not unusual to see Lionel spending the afternoon in his study standing at his desk, notebook in hand, peering over his glasses at a problem, coat collar turned up, looking as if he had just arrived or was about to leave. It was in that study where his well-known "reproducible machines" had been constructed (Penrose and Penrose 1957) and where he created multiple wooden and other puzzles, among them *Puzzles for Christmas*, published together with son Roger (Penrose and Penrose 1958), their purpose "to provide mental stimulation during the academic vacation." The publication included the "impossible staircase," a famous theme in the work of Dutch artist Max Escher; it was the Penroses who, in correspondence with him, had given Escher the idea.

One evening in late autumn, the Prof and I happened to answer the front doorbell simultaneously. A strange young man with a foreign accent thanked us politely and headed confidently past us, into the hall and up

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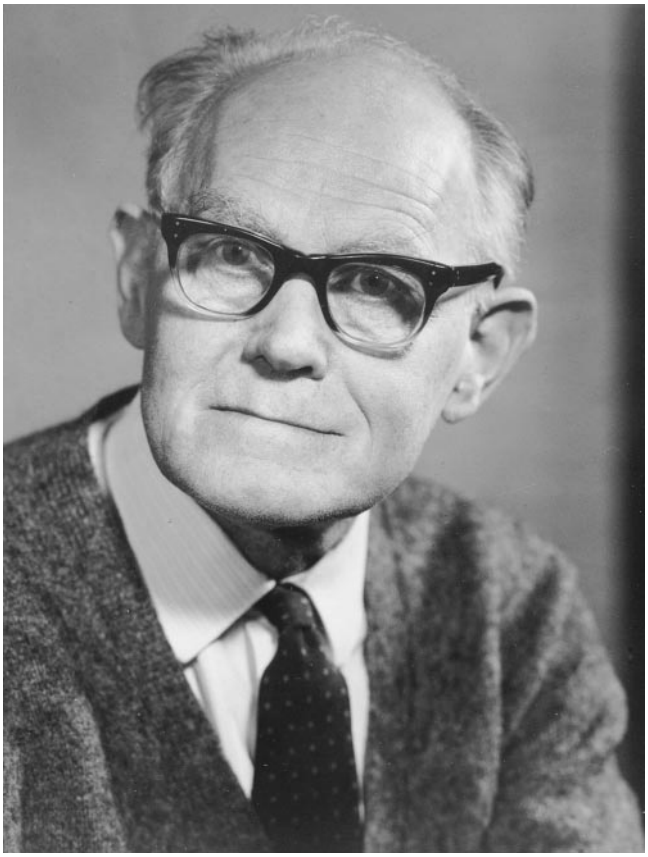

Figure 1.—Lionel Sharples Penrose, photograph about 1971. Photo by Godfrey Argent.

the stairs. In answer to the Prof's rather diffident question, he announced that he had lived in the house for over two weeks. He had met Mrs. Penrose in the street late one night and inquired about an address in the neighborhood where a room was available for rent. Rather than give him the complicated directions he sought, she invited him to stay at Rodborough Road. The trivial matter of informing her husband had slipped Margaret's mind.

On another evening during that same fall, the Prof knocked on the door of our room and invited me to his study. Someone wanted to meet me, he said. As I entered, he introduced me simply by my first name. A tall, slender woman came toward me with outstretched arms and, with tears in her eyes, embraced me warmly. I knew I had never seen her before, nor did I recognize either of her two male companions. "So fortunate, my dear," she said, noticing my completely bewildered and uncomprehending facial expression, "that Lionel has such a good memory. You see, I remembered the 'Renata' part and wondered whether it could possibly be you, but it was Lionel who knew your maiden name and so, of course, it *had* to be you!" I learned that the three visitors, like Lionel, his parents, and his family, were longstanding members of the Society of Friends (Quakers). It was they who in 1939 had organized the publication of a little booklet through which they appealed to their members and other British families to take care of a child seeking refuge from Hitler-occupied Europe. My photograph, at age 7, had been among those in the booklet. Twenty-nine years later Professor Penrose and his visitors recognized my somewhat uncommon name and realized that I had been among the hundreds of children for whom a British home had been found during World War II and whose lives they had helped to save.

Lionel Sharples Penrose was born on June 11, 1898, the second of four brothers. His father was an artist (a portrait painter); one of his brothers was a sailor, and another, Roland, was also an artist and according to family legend introduced Britain to the work of Picasso. For that, Lionel would later quip, Roland was knighted by the Queen. Lionel, the most academically minded of the four, studied the Moral Sciences Tripos (mathematics, philosophy, and psychology) at Cambridge; later, after spending a year in Vienna where he met and explored the work of Freud, Wagner-Jauregg, and others, he became interested in the psychology of mental illness and mental deficiency. However, to learn more thoroughly about brain physiology, Penrose realized that he needed to obtain a degree in medicine. He returned to Cambridge in the late twenties. His subsequent M.D. thesis and his interest in psychiatry resulted in an appointment in 1930 to the position of Research Medical Officer at the Royal Eastern Counties Institution, a residential facility for what was then called the "mentally defective" population. Penrose's charge was to study the causes of mental retardation, with funding provided by the Medical Research Council and the Darwin Trust.

The Colchester Survey, 1931–38: The Royal Eastern Counties Institution was located in Colchester in southeastern England, and Penrose's work there culminated in the incomparable classic, *The Colchester Survey: An Etiological Study of 1280 Cases of Mental Defect*, which became the basis for his lifelong work (Penrose 1938). His basic concept was that mental retardation (MR) and illness are biologically, not socially, determined. Hence his book *Mental Defect* (Penrose 1933a) and later three editions of *The Biology of Mental Defect*, the last in 1972 (Penrose 1972), are unsurpassed in their time for the wealth of original scientific, biological, and genetic information that they contained.

The Colchester Survey included evaluations not only of the residents of the institution but of both parents and siblings whenever available. It took 7 years to complete and contributed an enormous amount to knowledge about multiple aspects of mental retardation, most of which applies to this day. The work was done predominantly by Penrose and one co-worker, Miss D. A. Newlyn; it was prepared for publication by his devoted, loyal, erstwhile secretary, typist of manuscripts, later coworker, editor, and Cerberus of the office, Miss Helen

Lang-Brown. Every family of the 1280 residents of the institution was visited personally, sometimes more than once; family medical histories were obtained, records reviewed, and IQs tested in every available relative. There were 6629 siblings in addition to parents and other family members. The residents were carefully examined clinically by Penrose himself in an attempt to determine the causes of intellectual impairment in each individual. The end of the survey contains an appendix (still useful) providing detailed information about each of the 1280 propositi and their families. The most important conclusions include the predominance of males among the mentally retarded population, caused in large part, as we now know, by several genes on the *X* chromosome; the heterogeneous underlying causes of mental defect; the absence of any strict dividing line between mental retardation and "normal" intellectual functioning; the demonstration of the role of environmental as well as genetic factors in the occurrence of certain types of mental retardation (including Down syndrome); and the more frequent recurrence of mental deficiency among children of mildly as opposed to more severely retarded parents. Reproduction among the latter is rare, and causes of severe MR are often *de novo* chromosomal abnormalities or other spontaneous events.

The significance of increased maternal age in families of patients with Down syndrome, which is perhaps among Penrose's best-known discoveries, was mentioned briefly in the Colchester Survey, as were many other topics that subsequently formed the subjects of separate publications in which they were explored in greater detail. For example, the 20 patients at Colchester who had epiloia, or tuberous sclerosis (TS) as it is now better known (an autosomal dominant neurocutaneous disorder characterized by skin changes, seizures, usually benign tumors, and mental retardation), became the basis for the observation by Penrose not only of variable expression in multiple affected members within a single family, but also for one of the first direct estimates of mutation rate in humans. In considering variable expression, Penrose postulated that there had to be "modifier" genes at different loci that altered the expression in different family members. He also observed some individuals who had no other affected relatives within their family, and he suggested that this could be the result of a "fresh" mutation. As the incidence of TS in the mentally retarded population was estimated to be around 1 in 300 and the incidence of MR in the general population about 1%, the incidence of TS in the general population was about 1 in 30,000. In Penrose's study, about one-quarter to one-half of the patients had no affected family members; thus, perhaps the new mutation rate was around 1/240,000 to 1/120,000. This was reported in a joint, now classical paper with Penrose's scientific idol, colleague, and predecessor in the Galton Chair at University College, London, J. B. S. Haldane, who had calculated the mutation rate in hemophilia by the indirect method (Haldane and Penrose 1935).

The discovery by Fölling in 1934 of imbecillitas phenylpyruvica, or phenylketonuria (PKU), the designation suggested by Penrose's co-worker, J. H. Quastel, led Penrose to search for patients with the disorder at Colchester. Aware of the characteristic "mousy" odor surrounding such patients, he would visit a room full of residents at any institution for the retarded, look around, sniff for a while, and head straight toward a patient who was usually—though, as Penrose carefully noted, not always—blue eyed and light haired and sitting in a bent-over position, with stereotypic busy "shoemaker-like" hand movements that distinguished him or her from those around. Since the metabolic block was known to be at the level of phenylalanine, one of the precursors of melanin, patients with PKU were initially thought to be fair skinned and blue eyed because of melanin deficiency. Penrose stressed, however, that since phenylalanine was not the only precursor of melanin and collateral pathways resulted in at least its partial production, the lighter coloring of patients with PKU was due only to a dilution of pigment compared with the rest of their family, not to its complete absence. He was among the first to suggest a diet of fruit, sugar, olive oil, and vitamins to treat it. It led to malnutrition, however, and had to be abandoned. It was at that time that he established, on the basis of several families with similarly affected siblings and one with consanguinity, that PKU was caused by an autosomal recessive gene (Penrose 1935).

Down syndrome, other aneuploidy, and dermatoglyphics: It was also at Colchester that Penrose's interest in people with Down syndrome was first aroused. They were easily recognizable and formed a more homogeneous group than many others who had mental retardation. The diagnosis was more common than any other and, above all, Penrose enjoyed these patients. He enjoyed their affection for him, and when they could speak, they called him by name. He never ceased to be amused by a story that he told repeatedly about a man with Down syndrome who lived at Harperbury Hospital, where Penrose worked after retirement. The man was walking along the drive and exclaimed to Penrose, with whom he was chatting, "Look, Dr. Penrose, there's another mongol like me, and over there, there are two—they must be bigols!"

There were 63 people in the Colchester Survey who had Down syndrome, and for the rest of his life Penrose studied them and the causes of their condition. Other families with members who had Down syndrome were also included in his investigations. He had initially found that there was a significant correlation between increased maternal and paternal ages and the birth of infants with Down syndrome. However, when he patterned his analysis after that employed by Sewall Wright

to assess the causes of polydactyly in guinea pigs (Wright 1926), Penrose determined that there was a highly significant partial correlation between maternal but not paternal age and the occurrence of Down syndrome. To confirm this conclusion further, Penrose used regression analysis to compare paternal and maternal ages, as well as mean maternal and paternal ages at the time of birth of Down syndrome and other offspring within families. After correction for parental age correlations, he found no significant difference between the means of observed and expected paternal ages at the birth of infants with Down syndrome and of other offspring, whereas the difference of the same parameters between those observed and expected for maternal ages was six times the standard error (Penrose 1933b). He showed that birth order, parity, and length of interval between pregnancies were not significant etiological factors.

Some 30 years later, after the discovery of chromosomal translocations, Penrose returned to his exploration of recurrence risks for Down syndrome within families. He studied "21/D" and "21/G" translocations and subsequently found that the maternal age effect did not apply to either of them. Moreover, he continued to be puzzled by the presence within some families of more than one person with nontranslocational standard Trisomy 21 and apparently normal parental chromosomes. It was Penrose's suggestion that mosaicism could perhaps account for these instances. He studied the dermatoglyphics of such parents, and by comparing them statistically with those in their offspring with Down syndrome, as well as with those in the general population, he concluded that about 10% of mothers of single children with Down syndrome and perhaps 50% of those with more than one were mosaic for Trisomy 21, even in the absence of other phenotypic or intellectual characteristics (Barnicot *et al.* 1963).

In 1971, one of Penrose's young co-workers, Peter Ohara (hired as an electron microscopy technician) was the first to observe neurofibrillary tangles in the brains of deceased patients with Down syndrome. Penrose of course immediately noted the connection with similar findings in patients with Alzheimer disease (Ohara 1972). Penrose's lifelong interest in Down syndrome is carefully documented in both editions of the classic, *Down's Anomaly* (Penrose and Smith 1966; Smith and Berg 1976).

The first instance of human double aneuploidy was described in 1959, shortly after Lejeune's report of Trisomy 21 in a patient who had both Klinefelter and Down syndromes (Ford *et al.* 1959). Penrose's curiosity about human malformation resulted in the observation of the first instance of human triploidy in an aborted fetus and, astonishingly, in the discovery of a 4-year-old girl with hemihypertrophy and few other physical characteristics who had triploidy in 30% of her blood cells (Penrose 1963a).

His continuous search for objective quantification whenever possible resulted in a related area of interest, which, like Down syndrome, was also to last for the rest of his life—namely, dermatoglyphics, a science that Penrose considered ideal for the study of normal and pathological variation within and between human and other populations. He contributed more to this area than anyone else in the world, but as the study of dermatoglyphics is rarely used in the current highly technological climate of medicine, I do not discuss it here. Suffice it to say that his most significant contribution was probably the discovery of a negative correlation between the number of *X* chromosomes and the total dermal ridge count. In other words, he found that, for example, infants with Turner syndrome (a chromosomal complement of 45,*X*) had the highest ridge count, whereas those with 49,*XXXXX* had the lowest (Penrose 1968).

Paternal age effects: The effects of parental age upon the occurrence of abnormalities in offspring never ceased to intrigue Penrose. It was Weinberg who first noted the phenomenon in 1912, and there were others who suggested that it was the father's not the mother's age that played a significant role in the occurrence of infants with, for example, achondroplasia. However, it was Penrose who, again using the partial correlation method employed by Wright, provided the data to prove the hypothesis. His results were a mirror image of those found in families with Down syndrome. In other words, if the maternal age was kept constant, a significantly positive correlation (+0.273) was found between the paternal age and the incidence of achondroplasia, whereas the maternal age effect disappeared completely if the paternal age was regressed out. Furthermore, Penrose noted that the statistical significance of the paternal age effect increased considerably when nonsurviving infants with achondroplasia were excluded from the calculations (Penrose 1955, 1957). It is possible, although no proof exists from the old data, that the infants with "achondroplasia" who died neonatally or shortly thereafter had different diagnoses of more severe, perhaps lethal, short-limbed dwarfing disorders. The survivors represented true instances of new (paternally derived) mutations of the gene.

Together with Haldane, Penrose also studied the paternal age effect upon mutations of genes located on the *X* chromosome. Haldane had accurately postulated an increased occurrence of hemophilia in the grandsons of older maternal grandfathers, implying another example of a higher mutation rate in males. Four decades later, it was Crow who finally completed the story by summarizing data showing that, at the molecular level, the rate for base substitutions (the cause of the achondroplasia mutation) is indeed higher in males than in females; he also showed that the phenomenon can be attributed partially to the larger number of cell divisions, estimated to be about 430 at age 30 in the male, as contrasted with the female germ line, in whom

there are only about 24 divisions from zygote to egg (Crow 1997a,b). More specifically, the mutation in achondroplasia, in the fibroblast growth factor receptor 3 gene (*FGFR3*) on *4p16.3*, consists of a single substitution of the normal glycine residue by an arginine residue at codon 380. This same Gly380Arg mutation is, surprisingly, present in almost all of the hundreds of patients with achondroplasia who have had mutational analysis to date, and it is of paternal origin in those in which the parental origin could be determined (Horton 1997). Thus, we owe our understanding of the paternal age factor, its causes as well as underlying mechanisms, to the imaginatively creative minds of three generations of genetics heroes.

Mental illness, 1939–45: As a member of the Society of Friends, Penrose was a conscientious objector and, although he had driven a Red Cross ambulance during World War I and helped to rescue many wounded soldiers from the trenches, it was not a period in his life that he particularly enjoyed discussing. In 1939, after completion and publication of the Colchester Survey and at the beginning of World War II, Lionel, Margaret, and their then three children, Oliver, Roger, and Jonathan, emigrated to London, Ontario, where they stayed for the next 6 years. All three sons, as well as their younger sister, Shirley, born after the war, have made remarkable contributions to science in their respective fields. Oliver, a Fellow of the Royal Society (FRS), is a professor of mathematics and physics; Roger, also a third-generation FRS (after his father and maternal grandfather), now knighted, received the Field prize for mathematics at a very early age; Jonathan, a professor of psychology, was the British chess champion for 10 consecutive years; and Shirley is a distinguished pediatrician and clinical geneticist.

After the arrival of the family in London, Ontario, Penrose was appointed to the position of Director of Psychiatric Research for the Province of Ontario. He gathered data on some 1600 patients, their ages at onset of mental disease, parental ages at birth and onset of disease if applicable, medical histories, and IQs. He used his own nonverbal "pattern perception" test to discriminate between mentally ill and otherwise affected individuals and to compare parent and offspring IQs. These and other data from the Canadian years, published in meticulous tables and appendices, have become the basis for recent studies on evidence for paternal transmission and anticipation in schizophrenia (Bassett *et al.* 1997).

The Galton Chair, 1945–65: After the war, Penrose was appointed to the Galton Chair of Eugenics and to the directorship of the Galton Laboratory at University College, London. The professional pedigree of the chair was auspicious. Established by Francis Galton in 1911, it was first occupied by Karl Pearson until 1933, when he was succeeded by R. A. Fisher, who held it until 1943. At that time J. B. S. Haldane, who had been head of the Department of Biometry since 1935, became the head of a united department of Biometry and Eugenics, with Penrose in the Galton Chair from 1945 until his retirement in 1965 at age 67. In 1957, when Haldane moved to India, Penrose became the head of a department called Eugenics, Biometry, and Genetics. He hated the word Eugenics and the philosophies with which it had become synonymous. He said it was "irksome" to be the head of a department of Eugenics and to edit a journal with Eugenics in its title without ever studying or writing a word about eugenics! But it was not until 1954 that he succeeded in officially changing the title of the journal he edited from *Annals of Eugenics* to *Annals of Human Genetics*, and it was only in 1963 that his chair finally became the Galton Professorship of Human Genetics.

The group assembled around Penrose and Haldane in the '50s and '60s, which included several brilliant, enthusiastic, and self-motivated young postdocs, became the future founders of British, European, and some American medical genetics dynasties. A possible reason for this was that Penrose was among the first geneticists of his generation to be medically qualified; hence many of the topics that he selected for study had future medical implications. So, for example, Harry Harris, Penrose's successor to the Galton chair, used paper chromatography as well as gel electrophoresis in the early days to study normal and abnormal polymorphisms in human blood and urine.

Cedric A. B. Smith, the humblest of individuals, was a brilliant mathematician and, according to Penrose, was the firm base upon which the post-war laboratory's reputation was built. For example, Penrose and Smith together simplified the "discriminant function" method of Fisher, conventionally used to discriminate between two populations on the basis of measured characteristics (Penrose 1945). The older method was cumbersome and required the inversion of the variance-covariance matrix, a calculation that even today is accomplished by computer (then unavailable). Penrose, with Smith (although each gave the other the major credit), devised a method whereby no matrix inversion was required, only a calculation of the difference D between the population means. The loss of efficiency was small (when based on assumptions of normality of distribution). In a later paper, Penrose (1954) pointed out that the generalized distance between two populations was (approximately) simply the sum of the "size distance" and "shape distance."

Always interested in family as well as population investigations and their formal mathematical analysis, Penrose strongly encouraged linkage exploration despite, as he wrote, "discouraging odds against finding evidence for two genes on the same human autosome" (Penrose 1967). Three linkages were established in relatively rapid succession, including that by Jan Mohr of Denmark (Lutheran blood groups and secretor status), Syl-

via Lawler and Jim Renwick (nail patella syndrome and ABO blood types), and Elizabeth Robson and Harry Harris (transferrin and serum cholinesterase).

Birth weight was another quantifiable, ubiquitous, and variable parameter, applicable to individuals and families, as well as populations, and therefore another obvious target for Penrose's curiosity. Together with M. N. Karn and others, he collected an enormous quantity of data and attempted to correlate birth weight and parity, length of gestation, maternal (and paternal) age, infant survival, etc. They established, among other findings, a genetic tendency toward high (10 lb or more) birth weight in some families (Karn and Penrose 1961).

Julia Bell, one of Penrose's co-workers at the Galton Laboratory, was a population geneticist interested in the genetics of human disease. She analyzed data from families with dystrophia myotonica (DM) and other diseases (Bell 1947). Although Penrose had great respect for his elder colleague and visited her regularly late into her 90s, he disagreed with her conclusions, which indicated increasing severity and earlier age of onset in successive generations of families with DM. This concept, known as anticipation and defined as a process of progressive worsening of hereditary disease in successive generations, with an earlier onset in offspring than in parents, was initially considered by Penrose to be an artifact of ascertainment rather than a phenomenon of direct biological significance (Penrose 1948). It took over 40 years to provide one mechanistic explanation of anticipation. It can be explained by unstable DNA, consisting of trinucleotide repeats that increase in number in some families in successive generations and sometimes correlate with the severity and earlier age of onset of disease (Sutherland and Richards 1992).

On the other hand, a myth about *Y*-linked inheritance really did exist and, before 1958 when Penrose and Curt Stern dispelled it (Penrose and Stern 1958), it was mentioned in genetics texts as the only example of that form of inheritance in men. It concerned a family of allegedly six consecutive generations of "porcupine" men (the Lambert pedigree) whose bodies were covered with "half-inch scales," sparing face, palms, and soles. Transmission was from father to all sons, with all daughters described as unaffected. Penrose and Stern conclusively showed that the actual family consisted of four, not six, generations with both affected and unaffected males and females and that the disorder, known as ichthyosis hystrix gravior, was inherited through a mutant autosomal dominant, not a *Y*-linked, gene.

In June 1948, Penrose gave a presentation to a cancer symposium in London on the genetics of breast cancer (Penrose *et al.* 1948). He recognized the advantages of studying breast as opposed to other cancers, because it was more easily and accurately diagnosed than other primary tumors. It was common, of public health significance, and accounted for almost 3% of female deaths. Finally, it presented a mathematical and statistical challenge that Penrose addressed with a characteristically simple, yet logical approach.

In spite of the existence of compelling evidence in the form of three- and four-generation pedigrees, previous investigators had been unable to demonstrate a definitive hereditary component in breast cancer. Penrose and co-workers compared deaths from cancer (breast and otherwise) in the relatives of a series of 510 propositae, with the rate by age given in statistics for the general population (available in England and Wales since 1911), thus avoiding the need for a control group. Their second purpose was to attempt to determine the type of inheritance and to rule in or out the possibility of transmission through maternal milk or cytoplasm. Results showed that within the families of the propositae, the same disease occurred with significantly increased frequency in sisters and mothers (and one brother), as compared with the general population. The rate of nonmammary malignant disease was not significantly increased among relatives. The study concludes with an appendix, still useful today, that lists all 510 propositae (by number) with detailed three-generation family histories of breast cancer, including laterality (also found to be genetically determined), pathology, age of onset, and death.

During the Galton Laboratory years, Penrose's overriding interest was the study of patients with mental retardation. He "adopted" one of the large residential institutions for the mentally retarded, Harperbury Hospital, which was located northwest of London in what was then quite seriously called London's "lunatic fringe," now the "green belt." Such institutions were situated in all four directions from the center of London, hence the horrifying term. Harperbury had 1600–1800 residents, two-thirds of whom were male, and it was always Penrose's dream to be located in their midst so that he could study and evaluate them in individual detail.

In 1963, he received an international award from the Joseph P. Kennedy Jr. Foundation for his contributions to the study of mental retardation. He received the award from President Johnson personally in November 1963, shortly after the assassination of John F. Kennedy. A delightful handwritten account exists, entitled "Three trains, three planes, a ship and an etched piece of glass with a silver stand," in which he recorded his impressions of the voyage to America on the Queen Elizabeth II with Margaret and of the ceremony itself.

Issues of social and ethical importance were never far from Penrose's thoughts. Using sound mathematical reasoning, he rarely missed an opportunity for debate with his enthusiastic, eugenically minded peers about their erroneous conceptions of the proliferation of the poor, the mentally ill, and the retarded (*e.g.*, Penrose 1963b). He also studied crowd behavior and mass hysteria, mostly in connection with the Russian Revolution of 1917 or pre- and "peri"-war Nazi Germany. He sum-

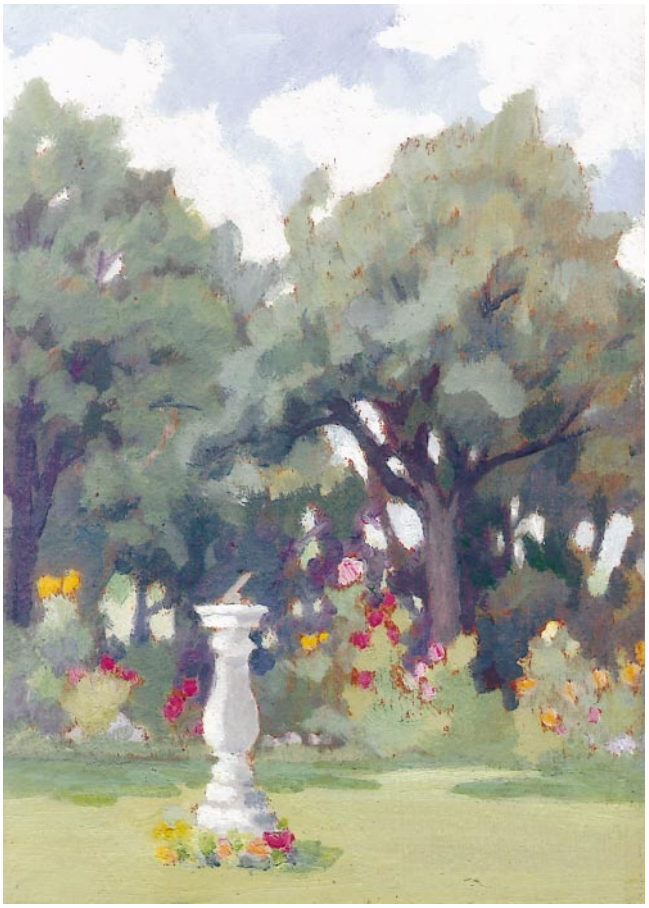

Figure 2.—Oil painting on wood of the grounds of the country house in Thorrington, by Penrose.

marized his ideas in a monograph entitled, characteristically, *On the Objective Study of Crowd Behavior* (Penrose 1952). Later, he published a leaflet, *Hazards of Nuclear Tests*, urging Britain, which he described as a "country aspiring to greatness," to seize the moment and benefit humankind by abandoning its military demonstration of atomic power. In the 1930s he and Margaret had been instrumental in cofounding the Medical Association for the Prevention of War, in which both were active for the rest of their lives.

In 1961, he proposed a more equitable mechanism for representational voting, using the United Nations as a paradigm. It was unfair, he wrote, that member states like Iceland, Switzerland, and India with populations of 150,000, 5 million, and 350 million respectively, had one vote each. Disregarding votes per capita, which would give no power whatsoever to small countries, Penrose proposed a simple model whereby the power of representative voters was inversely proportional to the square root of the total number of voters in each country. Iceland, Switzerland, and India would then have 1, 3, and 19 votes, respectively, while the United States and (then) Soviet Union would each have 13–14 (Penrose 1961).

The Kennedy-Galton Centre, 1965–72: When at age 67 he had reached the age of mandatory retirement from University College, Lionel finally saw the realization of his old dream. With the money from the Kennedy award, he established a laboratory and clinic within the grounds of Harperbury Hospital, which he named the Kennedy-Galton Centre for Mental Deficiency Research and Diagnosis.

Penrose's presence at Harperbury was of enormous benefit to the residents and their families, and a more sophisticated replica of the Colchester Survey with clinical, chromosomal, dermatoglyphic, biochemical, and other analyses was completed. It included a study of all females within the institution who had reproduced (1%) and of their offspring, providing a numerical estimate of empiric recurrence risks for "nonspecific" mental retardation, as well as an attempt at a comparable etiologic survey of mental retardation in the school-aged population outside the institution.

The Kennedy-Galton Centre became a mecca for visiting physicians and scientists. All were taken on an educational tour of the residents and acquainted first with them personally and second with their diagnoses. The patients, in turn, enjoyed a great deal of attention, and many of them began to exhibit skills (social, verbal, physical) that had previously not been observed in them.

The most famous of all, however, was Burt, the man with 48 chromosomes who had Klinefelter and Down syndromes. Everyone who came to visit Penrose was first taken to visit Burt to have a discussion about politics. He was the only son of parents who were academics and intellectuals. During our home visit with them, they confessed sadly that in the past they had had dreams for their son who, one day, could become a famous scientist or artist and make a contribution to the world. Instead, he would end his life, forgotten and unknown, in an institution for the retarded. At a memorial symposium for Penrose in the Hague in the fall of 1972, I

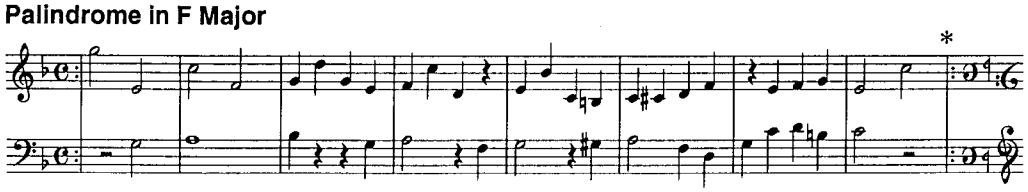

Figure 3.—Palindrome in F major, by Penrose.

showed a picture of Burt as an example of one of Penrose's Harperbury friends. The hum of immediate recognition was audible from the audience of some 2000 participants, and I wondered whether the picture of a famous scientist or artist would have evoked a similar reaction from an audience of comparable size. I regretted that Burt's parents were not present to witness his moment of triumph.

The Penrose family owned a lovely old Tudor house in the country in Thorrington, Suffolk, where they spent many weekends, frequently extending their exceptional hospitality to friends and visitors.

Lionel was, among other things, an accomplished artist, and the Thorrington gardens and surrounding countryside were frequent subjects for his oil paintings and his meticulous drawings (see Figure 2). He also played the piano and an antique spinet that stood in his study in Rodborough Road. He considered Bach to be the greatest of all musicians, and as, like many mathematicians, he was intimately acquainted with musical theory, he could analyze Bach's compositions with expertise, insight, and astonishing depth of knowledge. But not even music was safe from his fun-loving, irreverent mind, and his Palindrome in F major combines his ingenuity with his sense of humor (Figure 3).

He died suddenly, unexpectedly, on a Friday evening in May 1972, after having discussed his plans for next week's activities as always with the staff of the Kennedy-Galton Centre.

The 1973 monograph in the series *Biographical Memoirs of Fellows of the Royal Society* (Vol. 19, pp. 521–561) by Harry Harris, entitled *Lionel Sharples Penrose (1898–1972)*, which contains a complete Penrose bibliography, was a helpful resource in the preparation of this manuscript. Deep appreciation goes to Susan Johnson, who patiently typed and retyped with kindness, equanimity, and interest. Finally, I use this opportunity to thank Lionel, Margaret, and their four children for their contributions to the growth of my own family.

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