Lionel Sharples Penrose (1898–1972)

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Lionel Penrose was born in London on 11 June 1898. His father James Doyle Penrose (1862–1932) who was a portrait painter and his mother Elizabeth Josephine (Peckover) Penrose were both members of the Society of Friends (Quakers), as their ancestors had been for more than 200 years. He was the second of four brothers. They were brought up strictly according to the religious principles of the Society of Friends. On Sundays for example no games were allowed nor the reading of fiction, though the study of natural history and of astronomy in particular was encouraged. In later life though he remained a member of the Society of Friends he was not particularly zealous about religious meetings. However, his Quaker upbringing no doubt played an important part in determining his extreme dislike of show and pretentiousness and his pacifist outlook. Also he never acquired a taste for fiction.

He went to The Downs School at Colwall (1908–11) and then to Leighton Park School at Reading (1912–16). After leaving school he served in the Friends' Ambulance Train of the British Red Cross in France, and was demobilized after the end of the War in 1918.

He went up to St John's College, Cambridge, in January 1919, where he first decided to read mathematics, but soon changed to the Moral Sciences Tripos. This was partly because he wanted to study mathematical logic under Bertrand Russell, and partly because it offered the opportunity of studying psychology. However, it also involved doing philosophy which he always claimed he could never understand. In Part II of the Tripos he specialized in logic and obtained a First. He was awarded the Newcombe Prize and a Foundation Scholarship at St John's.

After obtaining his BA in 1921 he spent a year doing research in psychology with F. C. Bartlett and

then went off to continue his postgraduate studies at the University of Vienna. Here he did some work on memory and perception in E. Bühler's laboratory and also had the opportunity of meeting Sigmund Freud and other leading psychiatrists including Wagner Jauregg and Paul Schilder. At this time he attempted to write a thesis on the psychology of mathematics, but this did not get very far, and he became more and more interested in the problems posed by abnormal psychology and mental disorder. He came to the conclusion that to enter this field he must qualify in medicine. Decided on this course, he returned to Cambridge in 1925 to do the necessary preclinical studies (1st and 2nd MB) and then moved to St Thomas's Hospital, London for the clinical work. He obtained his medical degree in 1928. At St Thomas's he was awarded the Bristowe Medal for pathology.

After qualifying in medicine he obtained a research studentship to work at the City Mental Hospital in Cardiff. Here he was mainly occupied in studies on a patient with schizophrenia which formed the basis of a thesis for the MD which he obtained in 1930. In 1931 he moved again, this time to the Royal Eastern Counties Institution at Colchester where he obtained the appointment of Research Medical Officer, a position sponsored by the Pinsent–Darwin Trust and the Medical Research Council in order to foster research into mental defect.

The move to Colchester represented the starting point of his research career in human genetics and in mental retardation which he was to pursue for the rest of his life. In 1939 he moved to Canada to become Director of Psychiatric Research for Ontario. But he returned to England in 1945 when he was appointed to the Galton Professorship of Eugenics at University College London. In 1965 when he retired from the Galton Chair he became Director of the Kennedy–Galton Centre at Harpenden Hospital near St Albans where he continued to direct an active research programme till the end.

During the years after the war the subject of human genetics underwent a period of the most

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remarkable expansion and development, so that by the time of his death the subject was a very different one from that which he had taken up in 1931. He remained throughout a leading figure in the field and exerted a considerable influence on its development both by his own contributions and through his students. In his 20 years at the Galton Laboratory there was a constant stream of postdoctoral fellows particularly from the USA but also from other countries who came to work with him, and the critical approach to human genetics which he fostered consequently became widely disseminated.

He received many honours and awards. These included Honorary DScs from McGill, Edinburgh, and Newcastle and the Honorary MD from Göteborg; the Weldon Medal for Biometrics from the University of Oxford, 1950; the Albert Lasker Award, 1960; the International Award of the Joseph P. Kennedy Jr Foundation, 1964; the James Calvert Spence Memorial Medal of the British Paediatric Society, 1964; and in 1965 at the 18th World Health Assembly in Geneva he received the first annual award of the Leon Bernstein Foundation for research in mental subnormality. He was President of the Genetical Society of Great Britain 1955–58 and President of the Third International Congress of Human Genetics in Chicago in 1966. He was elected FRS in 1953, FRCP in 1962, and FRC Psych in 1971.

In 1928 he married Margaret, the daughter of John Beresford Leathes, FRS, Professor of Physiology at the University of Sheffield. They had four children; Oliver (b. 1929), now Professor of Mathematics at the Open University; Roger (b. 1931), now Rouse Ball Professor of Mathematics, Oxford, and also FRS; Jonathan (b. 1933) who is an International Chess Master; and Shirley Victoria (b. 1945), now a paediatrician.

The Colchester Survey

The work that Penrose was appointed to carry out at the Royal Eastern Counties Institution under the auspices of the Pinsent–Darwin Trust and the Medical Research Council was planned in 1930. The aim was to ‘increase existing knowledge in the causation of mental deficiency’, and it was decided that the first thing that had to be done was to carry out a detailed study of a large series of mentally defective patients of all grades and types from both the clinical and the genetical points of view. Although by that time mental defect had come to be recognized as a major social problem, there was very little firm scientific knowledge about its nature or causation. Mental deficiency was the Cinderella of the public health services, and classification of

patients was largely the product of legal and administrative decisions designed to achieve a convenient way of providing care within the existing framework of institutional and other arrangements.

The state, at that time, of what might be regarded as educated lay opinion about the causes of mental defect is well illustrated by a story Penrose delighted to tell about the official opening of a new wing at the Colchester Institution. The patron of the Institution was the King and it was hoped that a member of the Royal Family could be induced to perform the opening ceremony. The selected candidate after some negotiation was a Royal Duke, but it was stipulated by the civil servants who made the arrangements that he was not to be allowed to see any of the patients. The reason given for this precaution was that the Duchess was at that time pregnant. In the end it all turned out well. The Duke was greeted with enthusiasm by a guard of honour who proudly stood to attention to salute him. They were all patients who belonged to the hospital troops of Boy Scouts and Girl Guides. With some difficulty it had been possible to persuade the authorities that any prenatal impressions of imbecility from this source should they be vicariously transmitted to the Duchess would be innocuous.

Medical and scientific opinion was no doubt somewhat in advance of this. But little systematic scientific research into the medical and biological problems posed by mental defect had in fact been carried out, principally because the subject seemed too far removed from the mainstream of medical science, or indeed from the mainstream of psychiatry. Certainly there appeared to be few conventional career prospects in embarking on research in this field, but to Penrose the apparent disadvantages and difficulties were probably among its main attractions. He was never one to follow the herd. Furthermore, he seems to have perceived from the beginning that if the subject was approached quite objectively and without preconceptions, and if a careful and systematic collection of facts about a large array of patients of all grades and types and about their families could be compiled, then there would be for the first time a firm base on which a critical analysis of possible causal factors could be built. In particular he saw that if accurate numerical information about such things as parental age, birth order, stillbirths, and the incidence of particular abnormalities and different grades of defect among the sibs and other relatives of the patients were collected, then these could be susceptible to rigorous statistical analysis, an idea which was somewhat novel in medicine or psychiatry at that time.

In general the subject must have appealed because it provided scope for his earlier interests in psychology, mathematics, and pathology and also no doubt because it represented so much uncharted territory which could be explored in depth. It probably also had the added attraction for him that it was at the time a far from popular field. There was also the social significance of the subject and its human implications. He felt that an objective but sympathetic investigation carried out with scientific rigour, of people who had been classified as idiots, imbeciles, or feeble minded, could hardly fail in the long run to be of major importance in improving their lot. This philosophy was simply expressed in the following passage at the close of his first book *Mental Defect* which was written during his first two years at Colchester and published in 1933.

Since mental deficiency is not a clinical or biological entity, but only a legal concept useful for social and administrative purposes, the problems concerning the subject have both a social and political as well as a scientific and medical significance. From the scientific point of view, these problems can be coped with systematically after sorting out the different types of individuals to be found legally classified as mentally defective. But the problems have also to be tackled from the social point of view. We have to remember that there will always be, in any human society, brilliant people and simpletons, and what to do with the simpletons will always remain a social problem. This is a question which civilization has to face. A society which is ideally conducted will have to make arrangements so that the simpletons can find a useful purpose in their existence.

The Colchester survey was started in 1931 and took seven years to complete. It was a detailed clinical and genetic study of 1280 patients in the Royal Eastern Counties Institution. It represented an enormous amount of work, since as well as the investigation of the patients themselves, data on a very large number of their relatives had to be collected. The scale of the study is indicated by the fact that the 1280 patients had 6629 sibs quite apart from their parents and other relatives.

The patients were all legally certified as mentally defective but they did not form a homogeneous group, and had been institutionalized by a variety of routes. Nearly half of them had been admitted at the request of the Local Mental Deficiency Authority and were of all grades and types. About 15% had been admitted to the so-called Charitable side of the Institution, about 6% had been originally admitted from the care of the Poor Law Guardians, and about 3% were privately supported. These were mainly graded as imbeciles or idiots. There were

also quite a number of patients (about 17%) who had been sent in by the Education Authority for training in the Institution's residential special schools. Finally, in about 10% of cases in the series, admission had followed some offence against the law, usually committed by the individual himself but occasionally by his parents. The patients were found to represent only about half of those who must actually have existed in the population which the Institution served. But different grades were represented disproportionately. It appeared that of the feeble minded nearly two-thirds had been admitted, but curiously enough of the idiots only about one-half, and of the imbeciles only about two-fifths.

The first problem was to grade each of the patients as far as possible in terms of their mental ability. This was mainly carried out by the Stanford–Binet and Porteus Maze tests which were in general use in the Institution. Taking the normal adult mental age as 14 years and calculating mental ratios on the basis of the test results, the patients were classified for purposes of analysis into four groups; dull, with mental ratios exceeding 70, simpletons with ratios between 50 and 69, imbeciles with ratios 20–49, and idiots with ratios 0–19. It was found that the gradings did not altogether match the legal gradings on which the patients had been certified. Thus as many as 14% of the total series of 1280 patients appeared to have mental ratios greater than 70, which would be regarded as falling within the range of normality. They had evidently become liable to legal certification as feeble minded because of anti-social or difficult behaviour. Simpletons also usually certified as feeble minded constituted 35% of the total, imbeciles 34%, and idiots 17%. The ages of the patients varied widely, the youngest being 4 years old and the oldest 70. But the average age was much the same in each of the four grades (about 24).

The patients were also examined in great detail clinically in order to classify them as far as possible into known diagnostic categories. Thus it was found that 63 of the patients were typical mongols, 50 suffered from congenital syphilis, 128 had various types of neurological disorder, 210 suffered from epilepsy, and so on. Penrose was however careful not to assume that the intellectual defect was necessarily caused by the particular clinical abnormality. In some instances this was obviously the case, but in others was probably only a part cause or possibly perhaps coincidental. Out of the 1280 patients only 308 had no definite signs of physical abnormality or mental disorder.

The most formidable part of the survey was the

family history investigation. The family of every case was visited on average two or three times by Penrose or one of his very small group of assistants. Facts were ascertained about the parents, sibs, and the patient's own children. Wherever possible the enquiry was extended to cover grandparents, uncles, aunts, nephews, nieces, half sibs, and cousins. Ages and dates of birth of parents, sibs, children, and grandparents were recorded. Miscarriages and still-births were also noted: and of course special attention was paid to specific clinical disorders in the family members.

Not only were the patient's relatives visited but information was obtained also from a great number of independent sources. The records of the voluntary associations for mental welfare were studied; public health authorities supplied information; education authorities were consulted; hospital records were examined, and so on. When all the available information had been collected, an assessment of mental grade for each relative was made on a scale intended to be comparable with the grading system used for the patients.

The family histories obviously varied greatly in extent and reliability. To facilitate detailed analysis and comparisons of different groups of patients, they were classified into three categories. The first included families in which reliable information had been obtained about all near relatives. Such histories were obtained in as many as 920 of the 1280 patients. The second category were those where the history was less reliable or incomplete in important details; for example where good information had been obtained about the mother and her relatives, but little was known about the father or his relatives. Out of 272 patients in this category, 62 were illegitimate. There remained 88 patients in whom the histories were very incomplete. Of these 28 were illegitimate. Anyone who has ever been involved in this kind of family investigation will recognize this degree of ascertainment of relatives as a remarkable achievement.

The detailed findings from the Colchester survey were published in 1938 by the Medical Research Council in their Special Report Series (no. 229). This report contains a mine of information and still remains a valuable primary source about many aspects of mental defect. It includes 62 tables in which the data are broken down in a great variety of ways to examine different points, and in addition there is an appendix giving the detailed information about each of the 1280 patients.

Some major general conclusions emerged from the report. Though now accepted without question they represented very important contributions

at the time. Perhaps the most significant were the absence of any sharp dividing line between mental deficiency and the so-called normal state, the evident heterogeneity of what was called mental defect, and the multiplicity of causes both genetic and environmental which could be involved in its causation. At the end of the report Penrose remarked:

It has never seemed at all probable that a single cause could account for all mental deficiency in the same way that the *Spirochaeta pallida* accounts for all syphilis. The aetiology of mental defect is multiple and a facile classification of patients into primary or secondary, endogenous or exogenous, cases would have only led to a fictitious simplification of the real problems inherent in the data.

Another result of general importance concerned the overall incidence of mental defect of different grades among the immediate relatives of the propiiti. In the total data the incidence of defect among the parents and sibs of patients was estimated to be as high as 7-9%. This exceeded the estimate for the population in general by 6-8%. However, mental defect was found to be more common among parents and other relatives of simpletons than among those of idiots, though the defects that occurred in the families of idiots were more likely to be idiocy than of the simpleton grade. Thus, on the one hand, there was a general tendency for the sibs of idiots to be more intelligent than the sibs of higher grade patients; on the other hand, a larger proportion of idiots was found among the sibs of idiots than among the sibs of any other grade. It was also noted that there were many more mentally defective mothers than fathers, but for a number of reasons it was concluded that this probably did not represent a genetic phenomenon. For instance, the care of a defective child depended more on the grade of the mother than the father, and inefficiency in a mother was more frequently a decisive factor in persuading a local authority to take action to certify.

In the course of the work at Colchester a series of specific problems concerning particular types of patients were investigated and where necessary data on further patients from elsewhere were collected. Much of this work was published as separate papers and only referred to briefly in the final report. It included the now classic analyses of maternal age, paternal age, and parity in mongolism which will be considered later and also work on epiloia, phenylketonuria, the sib-pair method for detecting autosomal linkage, and a variety of other topics (see the Bibliography on p. 20). In addition he wrote two monographs. *Mental Defect* published in 1933 gives a critical appraisal of the state of the subject at that time. A comparison of

this with the fourth edition of his later book, *The Biology of Mental Defect* published in 1973, gives a remarkable picture of the developments that took place during these 40 years. *The Influence of Heredity on Disease* (1934¹⁹) was based on an essay for which he was awarded the Buckston Browne prize by the Harveian Society. It provides an interesting account of the analytical methods then available in medical genetics.

The work on the genetics of epiloia (1935²⁷) is of interest for two reasons. It was one of the first attempts to get to grips with the problem of the genetical basis of variation in manifestation of a human disorder apparently determined by a single abnormal or mutant gene. It also led to one of the earliest estimates of mutation rate in man.

Epiloia or tuberous sclerosis as it is now more often called is a condition with very variable clinical manifestation. Typically there is a characteristic rash on the face known as sebaceous adenoma, the occurrence of multiple nodules in the brain, and epilepsy. Some of the patients are idiots or imbeciles, but others are less severely retarded and still others fall within the normal range. Other pathological manifestations also occur and the patients vary greatly from one to another. Detailed data obtained by family visiting were obtained on the relatives of some 20 patients with the condition. Some of these relatives were also found to have the condition and for purposes of analysis the various cases were classified on the basis of the clinical findings into severe and mild forms of the disorder. The familial distribution observed could most simply be accounted for by the hypothesis that the condition was determined by a single autosomal gene for which the patients were heterozygous. Both mild and severe forms might occur among the affected individuals in a single family, but there appeared to be a positive correlation between the degree of severity of the condition in a parent and the degree of severity of the condition in the affected children. Since there was no indication that environmental factors influenced the degree of severity of the condition, this was interpreted as indicating the occurrence of common genetic 'modifiers'. If so, such 'modifiers' were likely to be at gene loci other than the locus occupied by the so-called main gene since no such correlation would be expected if the 'modifiers' were allelic. However, it was also found that in a proportion of the propositi neither parent and no other relative was affected and it was argued that these patients were likely to be the consequence of fresh mutations. The concept of genetic modification had recently come to the fore because of the work of Timofeef-Ressovsky on the

varying manifestation of certain inherited characteristics in *Drosophila*, and R. A. Fisher had discussed the evolutionary importance of processes of this kind. In a subsequent paper (1936²⁹) Penrose developed the mathematical theory of the concept as it might apply to human populations and also considered the human data in the light of Fisher's theory of the evolution of dominance. This paper, which considered the inheritance of human diseases in terms of population genetics and evolutionary theory, represented an important new departure for genetics in relation to medicine.

The estimation of mutation rate (1935²⁴; 1935²⁷) to the gene determining epiloia was arrived at in the following way. The observed incidence of epiloia in institutions for the mentally defective was about 1 in 300. Since the incidence of mental defect in the general population was about 1% the incidence of mentally defective individuals with epiloia in the general community would be about 1 in 30,000. The family data suggested that between one quarter and one half of the propositi were due to fresh mutations. Thus the mutation rate per individual per generation would lie between 1 in 120,000 and 1 in 60,000. This was probably an underestimate because some mutants would be expected not to exhibit mental defect and so would not have been included in the sample of propositi. This appears to have been the first estimate of mutation rate in man using the so-called direct method. At about the same time J. B. S. Haldane obtained an estimate of the mutation rate to the gene determining haemophilia using the so-called indirect method. They reported their results jointly in *Nature* (1935²⁴) and at the time it was thought that this was the first information available about mutation rates in vertebrates, and indeed it served as the starting point for much subsequent work. However it was found, though many years later, that the indirect argument had in fact been first used by Danforth in 1923 to estimate the mutation rate of another condition in man, but he had published in a rather obscure journal (*Eugenics, Genetics and the Family*, 1923, 1, 120).

In 1934 Fölling reported the discovery that certain patients with a severe degree of mental defect excreted large amounts of phenylpyruvic acid continuously in their urine. He called the condition 'imbecillitas phenylpyruvica'. This was the first clear example of a so-called 'inborn error of metabolism' to be identified since the classical work of A. E. Garrod in the first decade of the century and it represented a major advance for both human genetics and mental deficiency. Penrose immediately appreciated the significance of the discovery and set

about searching for further examples of the condition among his Colchester patients. After testing the urines of more than 500 he picked up his first case, a 19-year-old male idiot (1935²³). A brother of the patient, also an idiot though not in the Institution was also found to have the same condition. Other cases were subsequently identified (1935²⁶) and family studies supported the idea that the disorder was inherited as an autosomal recessive. The identification of the phenylpyruvic acid in the urine was confirmed for him by J. H. Quastel and also by H. A. Krebs. With Quastel he then proceeded to carry out one of the earliest metabolic studies of the disorder (1937³³). They devised rapid and reasonably accurate methods for estimating phenylpyruvic acid in urine and then proceeded to assess the effects on the rate of excretion of phenylpyruvic acid of feeding various substances such as phenylalanine, tyrosine, alanine, and phenylpyruvic acid itself to the patients and to controls. They showed that feeding L-phenylalanine to the affected patient led to a greatly increased urinary output of phenylpyruvic acid, but this did not occur in the controls. However, they noted that not all the additional phenylalanine administered was transformed to phenylpyruvic acid. They also showed that the rate of excretion of phenylpyruvic acid was not significantly affected by the administration of tyrosine or alanine, but it was greatly enhanced in the affected patient by giving phenylpyruvic acid itself. At the time the biochemical methods available to them were extremely limited and it was not possible for them to pursue the nature of the metabolic disorder further. It was Quastel who first proposed the name 'phenylketonuria' for the condition (1935²⁶) and this has since become universally accepted.

Even at this early date Penrose saw the possibility that it might eventually prove possible to treat the condition by administering a phenylalanine-restricted diet. One of the first diets he tried consisted of fruit, sugar, and olive oil with vitamin pills added. Very soon the phenylpyruvic acid disappeared from the urine. But trouble started after about two weeks when the patient began to lose weight because of the poor nutritional content of the diet, and the excretion of phenylpyruvic acid began again. Penrose consulted F. Gowland Hopkins at Cambridge about the possibility of constructing a nutritionally adequate phenylalanine-restricted diet. But Gowland Hopkins estimated that it would cost £1000 to produce sufficient for one patient for one week. So the matter had to rest. It was not till many years later that the dietary treatment of phenylketonuria was taken up again by others, this time with more success, and eventually

suitable diets became available commercially at more reasonable prices.

Mongolism

The group of patients known as mongolian imbeciles or mongols attracted Penrose's attention from his earliest days at Colchester, and he was to study them from one point of view or another for the rest of his life. They had a very characteristic clinical appearance and could in most cases be readily distinguished from other forms of mental defect. Furthermore, they were relatively common. There were 63 examples in the Colchester series and it was not difficult for him to find additional cases to study elsewhere.

Nothing was understood about the causation of the condition. But it had long been known that mongols were more frequently born to elderly parents and more frequently occurred towards the end of a family, often being the youngest child. However, the relative importance of maternal age, paternal age, and birth rank as aetiological factors was obscure as maternal age and paternal age tend to be highly correlated, and the later birth positions in a family occur at higher parental ages. Penrose set out to disentangle these effects.

He first considered the relative influence of maternal and paternal ages (1933¹⁵). He had by this time collected accurate data on parental ages in 150 families each containing a mongol child. There were in all 154 mongol and 573 normal children. He found as expected that there was a highly significant correlation between maternal age and the birth of a mongol child and also between paternal age and the birth of a mongol. He then applied the partial correlation technique which had earlier been used by Sewall Wright to deal with a similar problem concerning the incidence of polydactyly in guinea pigs. He found that the partial correlation between maternal age and mongolism after eliminating the effect of paternal age was still highly significant, whereas the partial correlation of paternal age and mongolism after eliminating maternal age was negligible. Thus the result suggested that paternal age was not an important aetiological factor in the causation of mongolism. But characteristically cautious he noted that the partial correlation technique applied was open to certain objections, in part because of the hypothetical nature of the variable mongol-normal. So he devised another approach which besides being more precise did not present these difficulties. He calculated for the whole data the mean age of the mothers and the mean age of the fathers at the birth of the mongol children and at the birth of the normal children.

He also calculated for the set of families the regression of paternal age on maternal age and similarly the regression of maternal age on paternal age. Using these regressions he could then estimate the expected paternal ages for the mongols and the normals assuming that the maternal ages were fixed. Similarly he could estimate the expected maternal ages assuming that the paternal age was fixed. The result was clear cut. The differences between the expected means of the paternal ages for the mongols and the normals did not differ significantly from the difference between the observed means. In contrast the difference between the expected mean maternal ages for the mongols and the normals was clearly less than the difference between the observed means. In this case the difference between the expected and observed differences was nearly six times the standard error. Thus paternal age could be dismissed as a major aetiological factor in mongolism. A similar conclusion was reached independently by R. L. Jenkins in the USA at about the same time (*American Journal of Diseases of Children*, 1933, 45, 506).

Penrose then turned to the question of the relative importance of maternal age and birth order, which represented a much more difficult statistical problem (1934^{21, 22}). By this time he had accurate data on 217 sibships each containing at least one mongol. There were in all 224 mongols and 807 normal children in the sibships. He first showed that, as expected, late birth rank like maternal age was highly correlated with the birth of the mongols. But maternal age seemed to be somewhat more closely associated with the occurrence of the abnormality than high birth rank. It therefore seemed reasonable to proceed by testing the hypothesis that the probability of a mongol child depended on maternal age in some unknown manner, but that for any given maternal age it did not depend on birth rank. The problem was made difficult by the varying sizes of the sibships and by the mode of their selection for inclusion in the data. The first method he devised (1934²¹) led to the conclusion that the birth rank effect might be entirely accounted for by the effect of maternal age. However, the method was open to objection because of certain assumptions and approximations it had been necessary to make in the calculations. He then developed a quite different method (1934²²) which avoided these ambiguities, using an approach suggested by R. A. Fisher. With this method which involved a rather complex series of calculations it was possible to compare the observed numbers of mongols in any given birth rank with the number expected according to the hypothesis. It was also possible to test

whether the differences between the two sets of numbers could be reasonably attributed to random sampling error or whether they must be regarded as due to a residual effect of birth order. The result was unambiguous. The observed and expected numbers for each birth rank were in good agreement and it could be concluded with some confidence that birth rank as such was not an important aetiological factor in the causation of mongolism.

He also considered the question as to whether the length of the birth interval immediately preceding the birth of a mongol child was of aetiological importance, as had been suggested by some authors. He demonstrated that where a mongol birth was both preceded and followed by a normal birth, the birth intervals between the mongol and the preceding birth and between the mongol and the succeeding birth were not significantly different. If anything the interval between the mongol and the succeeding birth was slightly longer. Thus an increased birth interval, representing as had been argued a period of diminished fecundity, did not appear to be of any causal significance.

This very rigorous analysis of parental age and birth order firmly established the pre-eminent importance of maternal age in the causation of mongolism. However, Penrose recognized that this did not necessarily mean that maternal age was a significant factor in all cases. Indeed mongols are sometimes born to quite young mothers. A great deal of his subsequent work on mongolism was concerned with probing this aspect of the problem further.

Although the majority of cases of mongolism are sporadic, it had long been recognized that occasionally the condition occurred in two or more closely related individuals, though of course with a condition as common as mongolism this might well have been attributable to chance and need not necessarily imply some genetical factor. A few examples of familial mongolism were encountered in the Colchester survey. Also some mongols were recorded among the relatives of the non-mongol propositi. It was found, however, that the incidence of mongolism was about 10 times greater among the relatives of the mongols than among the relatives of the non-mongol patients, and with the large numbers of relatives studied the difference was clearly significant statistically even though the absolute numbers of mongols among the two sets of relatives were quite small. The finding suggested that some genetical factor might indeed be involved. A suggestion which was strengthened by one particular family in which three sisters each had a mongol child and their mother's sister also had one.

An additional finding in this family, and one which he felt could hardly be fortuitous, was that the maternal ages for the mongol births were not apparently elevated (1938³⁶). Penrose pursued the problem of maternal age in familial mongolism persistently in subsequent years, and in 1951 published a detailed analysis of all the material then available¹¹⁹. It included besides the data he had been able to collect himself, all the data reported in the literature as well as additional information supplied to him by a variety of workers. He showed that the maternal ages of cases of familial mongolism were on average significantly lower than in cases of mongolism taken as a whole, and that the effect was particularly striking where the apparent inheritance of the condition appeared to have been through the mother.

Various possible genetic hypotheses to account for the slight but evidently significant familial incidence of mongolism were worried over and analysed throughout this period (eg, 1939⁴⁵; 1951¹¹⁹; 1954¹³⁶); but no satisfactory explanation could be reached. Various approaches to the problem of the possible genetical basis of mongolism were tried, but though they failed to produce a solution some new facts emerged which were to become of considerable interest later. One of these approaches was concerned with the study of palmar dermatoglyphics (1949⁹⁶; 1954¹³⁵).

Mongol patients show a complex pattern of morphological peculiarities and there was some indication from previous work that certain of these peculiarities might occur more often among the normal relatives of mongol patients than in the general population. However, the observed effects were small and since the traits which had been examined like 'fissured tongue' and 'transverse palmar crease' were not readily susceptible to exact measurement, the conclusions seemed somewhat insecure. Penrose saw that what was required for such a study was a trait which could be treated metrically and which by itself was a good discriminant between mongols and normals. The patterns of the palmar dermal ridges were known to be unusual in mongolism and after some trial and error he chose the so-called *atd* angle of the palmar triradii as a convenient metrical trait for his purpose. The *atd* angle was defined as the angle subtended at the most distal axial triradius (*t*) in the palmar ridge pattern by the most medial triradius (*d*) and the most lateral triradius (*a*) on each hand. By simple palm printing procedures a permanent record of the dermal ridges could be obtained and the *atd* angle measured quite accurately. The measurements provided a continuous variable which

could be treated statistically. They also served as a good discriminant between mongols and random normals. Thus he found that if this were the sole means of diagnosis only 12% of mongol patients would have been misclassified. He collected palm prints on a control sample of 2046 individuals, on 235 mongols, and on 403 parents and 295 sibs of the mongols. In all 5958 hands.

The analysis showed a slight but significant deviation among the normal relatives towards the mongol values. For example, using an *atd* angle of 57° as a point of discrimination, he found that about 80% of mongols had values greater than this but only about 8.5% of the controls. Among the relatives just over 13% had angles greater than 57°, a small but significant difference from the controls. More precise metrical analysis gave the same result. Although the absolute difference between the mean values for relatives of the mongols and the controls was very small, it was statistically highly significant because of the large amount of data. It was also noted that the effect was most marked among the mothers and sibs of the mongols, but only slight and probably not significantly in the fathers. Also it was noted that the effect appeared to be enhanced in families where there were two mongols in the sibship. There seemed no doubt about the reality of the finding. Its explanation was, however, quite obscure, though it seemed to indicate that some genetical factor was at work.

The turning point in the study of mongolism came in 1959 with the discovery by Lejeune and his colleagues in Paris that mongols are trisomic for a small acrocentric chromosome. This discovery was made possible by the development of new techniques which enabled human chromosomes to be accurately studied for the first time. These techniques rapidly became simplified so that before long chromosome analysis became almost a routine procedure. As a result in the next few years a number of new facts about mongols were established which began to explain the puzzling nature of many of the earlier findings. Most mongols were found to have 47 chromosomes instead of the usual 46, the additional one being a small acrocentric designated No. 21. The trisomy for chromosome No. 21 evidently resulted from non-disjunction in gametogenesis and the marked maternal age effect indicated that this usually occurred in the mother rather than the father. Presumably the likelihood of non-disjunction increases with advancing maternal age. However, it was also found that a small proportion of mongol patients had 46 chromosomes but that one of them was abnormal and represented a translocation of a large part of No. 21 on to some other

chromosome, so that effectively the patient was trisomic for No. 21. In some of the cases both parents showed normal karyotypes, but in others one of them had only 45 chromosomes which included the translocated chromosome and only one other representative of chromosome No. 21. Since the translocated chromosome could be transmitted from such a carrier who is phenotypically normal to some of the offspring, the general phenomenon could explain at least some of the unusual pedigrees of familial mongolism which had previously been recorded.

A further phenomenon to be discovered was the existence of so-called mosaic individuals, in whom cells of the standard trisomic mongol karyotype occurred along with cells having the normal karyotype. Such individuals though often apparently normal in most respects might exhibit in some degree phenotypic traits common in mongolism. Penrose immediately appreciated that mosaicism might perhaps explain the dermatoglyphic deviations observed among the relatives of mongols. On the basis of his earlier dermatoglyphic findings he estimated that about 10% of the mothers of a single mongol child might be mosaics, and perhaps 50% of the mothers of two or more mongols (1963²¹⁶; 1964²²⁸; 1965²³⁰).

The chromosomal results as they steadily accumulated led him of course to re-examine the question of maternal age. He had long been aware that the maternal age distribution of mongolism tended to bimodality. In data from some populations there appeared to be two maxima, one at about 27 years and the other at about 42 years, though in most data there was merely a marked skewing of the distribution (1951¹¹⁹). The overall distribution could most simply be regarded as being made up of two different distributions. One would comprise cases in which maternal age is not a significant factor and would therefore correspond to the distribution of maternal ages in the general population. The other would represent cases in which maternal age is a major influence. On this basis he was able to estimate that the proportion of cases of mongolism uninfluenced by maternal age was likely to be a little less than 33% in England and Canada, but might approach 50% in Japan, the USA, and the USSR (1965²⁴¹).

The problem now was to analyse this further in terms of the chromosomal findings. The published data (1966²⁴¹) showed that no maternal age effect occurred in those patients (about 2–3% of all mongols) with a translocation between chromosome 21 and one of the D-group chromosomes. As these cases much more frequently have a carrier mother

than a carrier father this result helped to account for the earlier finding of lower maternal ages in familial mongolism when transmission appeared to be through the mother. Another class of translocation mongols in which the translocation was between chromosome 21 and another G-group chromosome gave a different and quite unexpected result. Here a strong paternal age effect was identified (1962²⁰⁸; 1966²⁴¹) but no apparent maternal age effect. Because this type of translocation only occurs in about 1% of all mongols, this paternal age effect had been hidden in the earlier studies (1933¹⁵) where inevitably data from all patients had been pooled together. Two other classes of mongols were identified in which maternal age did not appear to be significant. One class represented the products of the very rare situation where a mongol patient has given birth to a mongol child. The other consisted of mongols born to mosaic parents (1966²⁴¹; 1967²⁴⁹). Thus the cases of mongolism in which elevated maternal age appeared not to be of aetiological significance were evidently a heterogeneous group, though only a proportion of the total estimated number of such cases could be specifically identified. The causal factors involved in the remainder are still obscure.

It might be thought because of his insistence on the collection of exact factual data about mongols and on its detailed statistical analysis, that Penrose regarded these severely retarded individuals simply as convenient biological objects to study. But nothing could be further from the truth. From the very beginning at Colchester he was attracted and charmed by their usually good tempered dispositions, their liveliness, and their frequent liking for music. His feelings about them are perhaps best illustrated by a passage from his book *Mental Defect* published in 1933, where he was describing some of the characteristic signs of the condition, which he suggested might be regarded as remnants of fetal existence.

The name 'foetalism' could well be applied to the condition and this would be a more characteristic name than 'mongolism'. The peculiar temperament of the affected persons, their secret source of joy, may be akin to the sort of happiness which the foetus might be supposed to experience in its blissful intrauterine surroundings.

This was a somewhat florid passage for him, because his prose was normally very cautious and restrained. However that may be, he always seemed to derive a great deal of pleasure out of working with mongols and also playing with them. As far as he was concerned there was no question that they were each to be regarded as human beings in their own right.

He never cared for the term 'mongolism' since it had no aetiological or other relevance at all. In later years he preferred to use the name 'Down's anomaly' for the condition after J. Langdon Down who had first described it as a clinical entity in 1866 and also incidentally coined its inappropriate and misleading name.

Canada (1939-45)

In 1939 Penrose took up the appointment of Director of Psychiatric Research for Ontario, and much of his work during the next few years was concerned with mental disease rather than with mental retardation.

A major problem which had emerged at this time was the evaluation of the effects of the new forms of shock therapy which had recently been introduced for mental disease and which were already being widely applied at many different centres. The two most generally used were the insulin coma treatment and the metrazol-induced convulsion treatment later superseded by electric shock therapy. But the published results from different centres about the efficacy of these treatments varied extremely widely, largely because of varying standards of assessing the degree of severity of the disease and of what constituted improvement or recovery. It was apparent that to determine whether shock treatment did any good, a method of estimating the prospects of spontaneous improvement or recovery in the group of patients treated was required. Some quite objective assessment of improvement was also needed, and the simplest criterion seemed to be whether or not a patient had been discharged from a hospital after a given time, or conversely whether he still remained on its books. Using this criterion Penrose proceeded to devise a quite new procedure for evaluating the effects of the treatments. In the province of Ontario, records of all patients who had ever been admitted to the provincial mental hospitals were available at a central office. The essence of the new method was to compare the actual number of shock-treated patients occurring on the hospital books at a given time after treatment with the expected number calculated from a random sample of the total mental hospital population (1943⁵⁹). Tables were constructed from data based on more than 8000 case histories, which gave the chance of a patient still being on the hospital books at a given time in the future, taking into account the age at first admission, sex, and length of time since admission. It was then possible to compare the numbers of treated patients remaining on the hospital books after a given lapse of time with the expected numbers calculated from the tables. Data on some

1600 patients with one or another form of shock therapy were available, and the effects of treatment could be assessed after two years and also after three years of its commencement. The combined results indicated that there was a significant though modest positive effect of treatment. However, when the data were broken down by diagnostic category it was clear that the schizophrenics had hardly benefited at all; whereas there was a quite striking effect among the patients classified as having manic-depressive or involutional psychoses. A later analysis (1944⁶⁷) considered the effects of treatment after a lapse of five years. It now appeared that the number of treated patients still on the books of the hospitals was not very different from the numbers which would have been expected. It appeared that those who had benefited from shock treatment would have improved anyway and would probably have been discharged within five years, but that the treatment had speeded the recovery.

Other papers written during this period included an interesting discussion of the possible relevance of Fisher's theory of the evolution of dominance to the observed sex differences in the age of onset of certain forms of mental disease; an account of a non-verbal intelligence test, the so-called pattern perception test he had developed (1944⁶³); some experimental results aimed at finding a useful discriminant between psychotic and normal subjects (1946⁶⁵); and a study of assortative mating in relation to mental illness (1944⁶⁵; 1945⁷³).

He also published two intriguing papers about the relationship of the provision of mental health services to the incidence of serious crime in different countries (1939³⁹; 1943⁶⁰). In the first he used statistics from various European countries to show that there was an inverse relationship between the amount of accommodation provided in mental hospitals and the prevalence of serious crime in the different countries. In the second paper he used the available statistics from different states in the USA to show that there was a negative correlation between the number of admissions of mentally defective patients and epileptics to institutions in the different states and the number of prisoners received from the courts into state prisons. He also noted that in the Union of South Africa a similar effect was to be observed if one compared the European and non-European populations of that country. The number of inmates of mental hospitals per 1000 of the population was about four times greater for the Europeans than the non-Europeans. In contrast the number of prisoners per 1000 of the population was nearly six times greater for the non-Europeans than for the Europeans. 'Few Euro-

peans', he remarked 'would interpret the correlation between mental illness and white population as evidence of constitutional inferiority of mentality among the whites, though some might be willing to ascribe the large amount of crime in coloured populations to innate tendencies.' Later he often propounded the view that a useful index of the degree of civilization a country had reached might be obtained by dividing the number of people in mental hospitals and institutions for the retarded by the number of people in prisons.

The Galton Chair (1945–65)

Penrose returned to London in 1945 to take up the appointment of Galton Professor of Eugenics and Director of the Galton Laboratory at University College. The Chair had been originally established in 1911 with a bequest from Francis Galton who died in that year. Karl Pearson was the first Galton Professor. He had previously been Professor of Applied Mathematics, but he then became head of a new Department of Applied Statistics which incorporated the two existing laboratories for Biometrics and Eugenics which he had already started. The Eugenics Laboratory, later to become known as the Galton Laboratory, had been set up in 1906 with the purpose of collecting data on human inheritance and with studying the relative importance of heredity and environment in some of the fields which were stirring the sociologists of the day such as alcoholism, tuberculosis, and infant mortality. Karl Pearson continued as Galton Professor until his retirement in 1933. At this point the college decided to split the Department of Applied Statistics into two separate departments, Eugenics and Statistics, and R. A. Fisher was appointed to the Galton Chair and became head of the Department of Eugenics. In 1935, J. B. S. Haldane had come to University College and had a separate department of Biometry. However, when Fisher left the college in 1943 to take up the Chair of Genetics in Cambridge it was decided to form one department of Eugenics and Biometry, with Haldane as its Head. Penrose was appointed to succeed Fisher in the Galton Chair. Eugenics and Biometry were located at different ends of the college so, although administratively one, they continued to function for most purposes independently. Penrose got on well with Haldane and valued the association highly. However, he also appreciated the physical separation of the two groups, since it served to protect him to some extent from the immediate impact of Haldane's periodic explosions against the college administration and others.

Shortly before Haldane left in 1957 to go to India, Penrose became Head of the joint department now known as 'Eugenics, Biometry and Genetics'. He never liked the name Eugenics, because it seemed to him to be too much associated with uninformed and dangerous policies of racial purification, and eventually, but only in 1963, succeeded in getting the title of his chair changed to the Galton Professorship of Human Genetics. The long delay had been because of legal problems connected with the original wording of Galton's will. However in the preceding years he had side-stepped the difficulty by making sure that the printed heading on his notepaper was simply 'The Galton Laboratory, University College London'.

As Galton Professor he also succeeded to the editorship of the *Annals of Eugenics*. The journal had been originally started by Karl Pearson in 1925 and subtitled 'A journal for the scientific study of racial problems'. Later under R. A. Fisher the subtitle became 'A journal devoted to the genetic study of human populations'. Penrose altered the subtitle to 'A journal of human genetics' and in 1954 succeeded in getting the name of the journal itself changed to *Annals of Human Genetics*. It had become the leading academic journal in the subject and under Penrose's editorship continued to maintain its high reputation.

In 1945 when Penrose took up the Galton Chair the College was only beginning to become reassembled after the war, during which much of it had been evacuated to places outside London. There was a great deal of bomb damage and inevitably many makeshift arrangements. The Galton Laboratory consisted of a few rooms and virtually no equipment. In effect its research programme had to be rebuilt from scratch. Funds from the College for research activities in a subject which formed no part of the undergraduate curriculum were very restricted. However, Penrose was fortunate in obtaining generous support from the Rockefeller Foundation and this indeed was to finance much of the work of the Galton Laboratory during the next 20 years.

Penrose unlike his predecessors was medically qualified and was more directly interested in genetic problems as they related to medicine. Much of his work was in the tradition of the mathematical and statistical approach to genetics for which the Laboratory had previously been best known. But under his direction the work in human genetics became much more broadly based than in the past.

He continued of course with his work on mental deficiency, particularly mongolism, and to do this

effectively he established a close working relationship with Harperbury Hospital, an institution for the mentally retarded near St Albans, where he could see and investigate patients. However, he also initiated a series of major investigations into other aspects of human genetics.

One of these was a study of breast cancer. The aim was to find out whether the incidence of breast cancer among the immediate relatives of affected patients was greater than in the general population. Previous studies had mainly compared the incidence of the condition among the relatives of a set of *propositi* with the relatives of a set of controls. Although they had provided suggestive evidence of a raised familial incidence, the results were indecisive because of uncertainties about the accuracy of the control data which was inherently difficult to collect. Penrose had the idea of getting round this difficulty by making use of death certificates, so that the ascertained number of affected individuals among the relatives of the *propositi* could be directly compared with expected numbers derived from the Registrar General's data for the general population over the previous 30 years, of causes of death in each age group in different years (1948^{92, 93}). The death certificates were checked for detail against hospital records. Altogether information about the relatives of 510 patients with breast cancer was obtained, a considerable undertaking. The critical data concerned the mothers and sisters. Among 406 mothers who had died, 25 had had breast cancer whereas only 11.12 were expected from the mortality in the general population by age and year. Similarly among 307 sisters who had died, 23 had had breast cancer whereas only 6.97 were expected. Mortality among these relatives from other sorts of malignancy agreed well with the expected numbers derived from the Registrar General's data. Thus there was a clearly significant and specific familial concentration of the condition.

Another major investigation initiated in the early years at the Galton concerned the biometry and genetics of variation in birthweight. A considerable body of data was assembled which enabled detailed analyses to be carried out on the influence on birthweight of factors such as gestation time, maternal age, parity and also of genetic factors (1951^{115, 119, 121}; 1952¹²⁴; 1961²⁰⁴). Among the various interesting findings which emerged, one concerning the relationship of birthweight and infant survival was particularly intriguing and also somewhat unexpected. The lowest mortality rate was found to occur at birthweights appreciably higher than the mean birthweight of survival children; the optimal birthweight for both males and

females being close to 8 lb (3.6 kg). This was surprising because it might have been expected that as a result of natural selection, the mean would have been the most favourable value.

The combined data enabled Penrose to estimate the approximate contributions of different factors to the overall variation in birth weight (1954¹⁴⁰; 1961²⁰⁴). About 38% of the total variation appeared to be genetical in origin, some 20% being attributable to the mother's genotype and 10% to the genotype of the fetus. Of the remaining variance about 24% could be attributed to maternal health and nutrition, about 7% to maternal parity, about 1% to maternal age, and about 30% to unidentified intrauterine factors. This novel type of analysis of a particular aspect of human variation was of importance because of the complexity it revealed. It demonstrated the care clearly required in the consideration of any quantitative variable in man. Penrose was careful to point out that this partition of the causes of birthweight variation could only be taken to apply to a relatively stable western European community. In other circumstances such as famine or war, or in other parts of the world the relative contributions of the different components to the variation might be very different.

Papers on a variety of other topics in human genetics were also published in this period. One of particular interest was concerned with an idea widely held among medical people that there was some mysterious process by which certain hereditary diseases became progressively more severe in succeeding generations of a family (1948⁹⁰). This was known as 'anticipation'. Penrose showed that the apparent occurrence of 'anticipation' in pedigrees of inheritance diseases was in general a consequence of the manner in which the material had been selected and was not a phenomenon of direct biological significance. It was likely to be most marked in disorders where there was a particularly wide variation in age of onset, but where there was little or no correlation between affected parents and children in this respect. The argument was illustrated by an analysis of the published pedigrees of the autosomal dominant disease, dystrophonia myotonica, which appeared to exhibit the phenomenon to a particularly marked degree. He also noted another feature of this condition which tended to enhance the effect. This was that while the parent-child correlation with respect to age of onset was low, the sib-sib correlation was quite high. He argued that such a pattern of interfamilial correlations was what would be expected if the variation in age of onset was dependent on the

nature of the particular normal allele which occurred together with the abnormal gene which determined the condition.

Another important piece of work was the demolition of a long-established myth in human genetics. This involved the famous pedigree of ichthyosis hystrix gravior, the so-called Lambert pedigree, which purported to show that this particular condition was determined by a gene on the Y chromosome. The pedigree as then drawn appeared to cover seven generations and indicated that the condition was inherited directly from father to son, all the sons being affected but none of the daughters. It was reproduced in most textbooks of human genetics and was generally accepted as an authentic example of Y-linked inheritance. Many examples of X-linked inheritance were known, but this appeared to be the only Y-linked case. Hence its widespread citation and its almost universal use in teaching. Penrose had always been sceptical about the validity of the pedigree, but he only became actively interested on the matter in 1956 when Curt Stern spent a short sabbatical at the Galton Laboratory. Stern was preparing a new edition of his well-known textbook on human genetics and was proposing to include as before the Lambert pedigree. Penrose expressed doubts about its reliability and together they decided to see whether the pedigree could be authenticated. Stern took on the task of searching the early literature, while Penrose set out to search the original parish records in Suffolk where the critical members of the family had lived more than 150 years earlier.

The story had begun in 1732 with the publication by the astronomer John Machin in the *Philosophical Transactions of the Royal Society* (37, 299) of what he described as an uncommon case of discoloured skin. The subject was a boy aged 14. At birth he had been normal but within a few weeks his skin became covered with a rugged bark or hide and in some places with an innumerable company of warts or slender protuberances. His palms, soles, face, and head were free. The father of the boy, a Suffolk labourer was not himself affected, nor was the boy's mother, nor were his brothers and sisters. In 1755 a further account of the boy, now grown up, was given by Henry Baker (*Philosophical Transactions of the Royal Society*, 49, 21). He was named as Edward Lambert and had married and had had six children all of whom were affected in the same way. Only one, however, had survived, a boy then aged eight. The boy and his father were exhibiting themselves at the George Inn, Fenchurch Street, under the title 'The astonishing porcupine man and his son'. Twenty years later the son was still in

London on exhibition, but soon after married and went back to Suffolk. After the lapse of another 25 years two sons of his with the same condition were on exhibition, and subsequently these two brothers went on an extended continental tour, and they began to elaborate their history. They now said that their grandfather was an adopted child who had been brought from a distant land, either Australia or the Davis Strait. They also fixed the mode of inheritance of the condition by asserting that only the males in the family had been affected and they claimed to have seven sisters at home in Suffolk, all with perfect skin. Their tour of Europe started in about 1800, and subsequently Richard turned up in London again where he earned his living by showing himself as 'a new species of man'. They were examined by many physicians during this period and the condition was quite well documented.

This was the essence of the story as far as could be judged from contemporary records. The family had not been heard of for more than a hundred years. Penrose had the idea that a search of parish registers in Suffolk might well provide critical data about the details of the pedigree. The first question concerned the origin of the first 'porcupine man', Edward Lambert. He had presumably been born around 1717 and it seemed worth while trying to find out if he had been born in Suffolk, or if as his grandson's story went he had been an adopted child brought to this country from afar. Penrose set about systematically going through the diocesan records collected at Bury St Edmunds and it was eventually possible to identify the baptism of Edward Lambert on 15 December 1716 at the village of Sapiston. This disposed of the grandson's account. The next question concerned the sexes of the six children of Edward, all said to be affected like himself. Some casual hints in the early descriptions indicated Brandon as the likely place of their births. So the Brandon registers were searched. Evidence for exactly six children of the right parentage, baptized or buried there during the expected period was indeed obtained. Unfortunately for the traditional story, however, two of them were daughters. A search for the next generation led Penrose to north-east Suffolk. It turned out that John and Richard had had four more brothers and there was evidence that three of these were unaffected. It also appeared that they had only one sister and not seven as they had claimed and as was shown on the standard pedigree. Furthermore, it emerged that the porcupine men shown in the last two generations of the pedigree were also probably fabrications.

Thus a new pedigree was eventually constructed. It differed in many important details from the one

that had been handed down by tradition and copied from one text to another. In particular it no longer suggested Y-linked inheritance. The extensive searches of the parish registers was of course a very laborious undertaking in which Penrose was helped by his wife Margaret. As he wryly remarked in writing about it:

Until recently it was thought that outstanding problems of human heredity could be adequately investigated without moving from an armchair. This method is now believed to be inefficient. . . .

The late 1950s saw the emergence of methods for the routine study of human chromosomes, and Penrose immediately appreciated that this would open a new chapter in human genetics and also in mental deficiency research. He took up this new field of work with enthusiasm and set up a small group to work on cytogenetics at the Galton Laboratory. Among the various cytogenetic studies in the following years, three are specially noteworthy. One was concerned with an individual who showed the characteristic features of both mongolism and the Klinefelter syndrome and who was found to have 48 chromosomes (1959¹⁷⁶; 1960¹⁸⁷). He was trisomic for chromosome No. 21 and also XXY. Another important study led to one of the earliest descriptions of a translocation between chromosome No. 21 and one of the D-group chromosomes, resulting in familial mongolism (1960¹⁸⁹; 1961²⁰²). Another paper (1961¹⁹⁵) reported the occurrence of triploidy in an early abortus, an observation which was the forerunner of a further important line of work in human cytogenetics.

The discovery of other chromosomal abnormalities besides mongolism which appeared to be due to non-disjunction raised the question as to whether such abnormalities were also associated with increased maternal age. In an interesting analysis (1964²²⁶) of an extensive body of published data on sex chromosome anomalies, he showed that while a marked increase in maternal age was to be found with the XXY and XXX syndromes, no such effect occurred in the XO syndrome. Furthermore, he showed that the distribution of maternal ages in XXY and XXX was probably attributable, as in mongolism, to the occurrence of two groups of cases; one group being uninfluenced by maternal age and the other group being strongly influenced by maternal age, and indeed roughly to the same degree as the corresponding group in mongolism.

Theoretical Work

C. A. B. Smith writes:

Discrimination. Penrose was interested in the

statistical problem of discriminating between two classes of individuals on the basis of measured characters. This arises particularly in the use of psychological tests to discriminate between population A, say normals and population B, say psychotics, where the scores from various tests must be combined in the most suitable way (1945⁷⁰). The results are most concisely and easily expressed in matrix notation, although Penrose did not use this.

Let $\mathbf{q} = (q_1, \dots, q_m)^T$ be the vector of m measured characters, and $\bar{\mathbf{q}}A, \bar{\mathbf{q}}B$ the means in the two populations, with difference vector $\mathbf{D} = \bar{\mathbf{q}}A - \bar{\mathbf{q}}B$. If we suppose that the variance matrix $\mathbf{V}$ is the same in the two populations and that the distributions are Gaussian, then Fisher had shown that the most efficient discrimination between population A and B was achieved by considering for each individual with measurements $\mathbf{q}$ the value of the linear discriminant function $\Lambda(\mathbf{q}) = \mathbf{D}^T \mathbf{V}^{-1} \mathbf{q}$. This is simple to use, but its evaluation in the first place required the inversion of the matrix $\mathbf{V}$, which was then tedious (and still is without a computer). Penrose (1947⁸⁸) suggested that very good results could be obtained by assuming that all the correlations between the characters had a common value r . If we normalize all the characters to have standard deviation 1, then

$$\mathbf{V} = (1-r)\mathbf{1}\mathbf{1}^T + r\mathbf{1}\mathbf{1}^T$$

(where $\mathbf{1}^T = [1, 1, \dots, 1]$) and

$$\mathbf{V}^{-1} = (1-r)^{-1} [\mathbf{1} - r\mathbf{1}\mathbf{1}^T / (1-rm)]$$

for $\mathbf{V}\mathbf{V}^{-1} = \mathbf{1}$. Hence the linear discriminant becomes

$$\Lambda(\mathbf{q}) = (1-r)^{-1} \left[\mathbf{D}^T \mathbf{q} - \frac{r \mathbf{D}^T \mathbf{1}}{1-r+rm} \mathbf{1}^T \mathbf{q} \right].$$

Now if we write

$$P(\mathbf{q}) = \mathbf{1}^T \mathbf{q}; Q(\mathbf{q}) = m(\mathbf{1}^T \mathbf{D})^{-1} \mathbf{D}^T \mathbf{q} - \mathbf{1}^T \mathbf{q}$$

then it follows that (i) $P(\mathbf{q})$ and $Q(\mathbf{q})$ are linear functions of $\mathbf{q}$; (ii) $\Lambda(\mathbf{q})$ is a linear combination of $P(\mathbf{q})$ and $Q(\mathbf{q})$; (iii) under the assumptions we have made regarding the form of the variance matrix $\mathbf{V}$, $P(\mathbf{q})$ and $Q(\mathbf{q})$ are uncorrelated in both populations A and B; (iv) for any particular individual with measurements $\mathbf{q}$, the calculation of the values of $P(\mathbf{q})$ and $Q(\mathbf{q})$ require only a calculation of the differences $\mathbf{D}$ between the population means. No matrix inversion is required, not even the finding of a correlation.

Penrose called $P(\mathbf{q})$, $Q(\mathbf{q})$ respectively the 'size' and 'shape' of the individual with measurements $\mathbf{q}$. Hence we may proceed by calculating P , Q for each individual, and then treating the discrimination problem as one in two uncorrelated characters, P , Q , only. The arithmetic required is extremely

simple, the loss of efficiency is small, indeed negligible when it is based on assumptions of normality of distribution and equality of variance which rarely hold exactly in practice. In a later paper (1954¹³⁴) Penrose pointed out that this means that the Mahalanobis generalized distance between two populations is (to a good approximation) simply the sum of the 'size distance' and 'shape distance'.

Sib-pair Linkage Tests. During the 1930s a great deal of thought was put into the problem of how autosomal linkage might be detected in human families. One obstacle is that linkage only has an observable effect when at least one parent in the family is a double heterozygote, say $GgHh$. When such a parent is genetically GH/gh (so-called coupling phase) the effect of linkage is to increase the frequencies of children with GH or gh chromosomes, and to decrease the frequencies of children carrying Gh and gH . When the parent is Gh/gH (so-called repulsion phase) the effect of linkage is exactly opposite, increasing the frequencies of Gh, gH and diminishing those of GH, gh . Unfortunately, in general, coupling and repulsion are indistinguishable in phenotype and occur equally often in the population, so that on the average they cancel out, and a simple count of the frequencies of different types of children is uninformative. Penrose (1935²⁵) suggested a simple way out of this difficulty, by considering not single children but pairs of children (sib-pairs). If a pair of sibs are alike as regards one character, such as both dominant G , or both recessive gg , then when there is linkage they will tend to be alike as regards the other character, ie, more often both H or both hh than would be expected by chance. Similarly, if they differ in the G character (one G , one gg), they will tend to differ also in H . Hence linkage gives rise to an association among sib-pairs. Penrose noted that this test did not require any testing of the parents, and hence in principle might be applied to mass testing of schoolchildren. It can also (1938³⁴) be readily adapted to characters not inherited in a simple Mendelian fashion or to continuously variable characters. However, it has the disadvantage that, because the parents are not tested, or are ignored, data from highly informative matings, less informative, and uninformative ones are combined together—and this makes the method one of very low efficiency except in the rare case of very close linkage. Penrose later attempted to improve the efficiency of the method by weighting sib-pairs according to their informativeness (1946⁷⁹; 1953¹³¹). It is worth noting that if the parental genotypes are known, apart possibly from phase, then the weighted sib-pair count, with appropriate

weights, becomes identical with Fisher's 'u-score' procedure, which is statistically fully efficient for detecting linkage in large samples. However, the standard procedure now adopted for dealing with linkage in Mendelian characters is to calculate the log-likelihood or z -score curve and this has replaced u -scores and sib-pairs. It has the advantage of combining detection and estimation in the same calculation. But sib-pairs could prove valuable for dealing with graded characters or those not inherited in a simple Mendelian fashion. It is of interest that the first autosomal linkage found in man (Lu/Sec; Mohr, 1951) was originally detected using Penrose's sib-pair method.

The Supposed Decline in Intelligence. Because of an apparent negative correlation between measured intelligence and fertility it was often argued that the average intelligence of the population is declining and that eugenic measures should be applied to counteract this. Penrose was sceptical about the theoretical basis of this argument. To illustrate his doubts he devised a model of a population in which there is a negative correlation between intelligence and fertility, but in which the mean intelligence remains unaltered in successive generations. This model is admittedly artificial, being based on a pair of alleles in which AA individuals are of slightly superior intelligence (IQ 103) but lowered fertility (1.89), Aa individuals are of low intelligence (IQ 73) but high fertility (4.00), aa are infertile idiots, and there is completely assortative mating. Later (1955¹⁵²) the model of a population in equilibrium was much further elaborated and made more realistic. It is shown that by taking 10 pairs of autosomal additive genes, values of the relationships between IQ, fitness, and mean number of sibs can be obtained which correspond quite reasonably well to those actually observed (though there are discrepancies at the ends of the range). This seems to substantiate quite clearly the point that the observations do not logically imply that intelligence must decline—indeed actual comparisons seem to indicate rather a very slight increase, though whether this is due to genetical or environmental causes is not clear.

The possibility of maintaining polymorphism in a population in stable equilibrium through heterozygote advantage (heterosis) fascinated Penrose and he considered the question further, mainly from the theoretical point of view, in other papers (1954¹³⁷; 1955¹⁵²; 1959¹⁷⁹; 1964²²⁴; 1972²⁹²).

Statistics of Majority Voting. Penrose was interested in the mathematics of voting behaviour

(1946⁷⁷; 1952¹²³). He was impressed by the fact that if each voter votes for or against at random with equal probability then the standard deviation of the majority in a society of n members will be $\sqrt{n}$. Hence if there is a determined group of individuals of size of the order of $\sqrt{n}$, it will have a high probability of carrying the vote its own way. He developed this theme. In particular, he argued that for a federal society divided into sub-societies (eg, the states of the USA, or nations in the UN) the equitable procedure was for each sub-society to have a number of votes as nearly as possible proportional to the square root of the number of its members. The mathematical logic of this is not too clear, but intuitively the suggestion has great appeal—it will avoid the absurdities of the two extremes, in which on the one hand very small states have an equal vote with large ones, and on the other hand when the votes are proportional to the population, the small states are virtually powerless.

The Self-replicating Machines

Roger Penrose writes:

No account of Penrose's scientific work could be complete without some mention of the various mechanical devices that he made, including a most extraordinary series of wooden self-replicating machines. Often he illustrated his scientific ideas by means of working models. For example, he made a family tree with a sliding part to illustrate in a graphic way the phenomenon of 'anticipation'; he made an elaborate multiple slide-rule for evaluating fingerprint ridge counts in connection with the diagnosis of Down's disease; he even made a life-like wooden bust of a microcephalic idiot. Frequently these models would be aids to clarifying his own thoughts as much as demonstrations for others. But there is no doubt that major influence in driving him on in this direction was his sense of fun and sheer enjoyment in constructing things from wood and other materials. For example, he enjoyed designing puzzles for both children and adults, and in particular he made a large number of assembly puzzles based on a theme whereby assembly had to be achieved with three or four parts sliding together simultaneously. The solving of such puzzles therefore required a certain manual as well as cerebral dexterity.

His facility with the design of wooden locking mechanisms stood him well when it came to the design of his series of self-replicating machines. The purpose behind these models appears to have changed somewhat as the designs evolved, but the first model (1957¹⁶³) was aimed at demonstrating

that exceedingly simple assemblages of shapes could be made to reproduce themselves under suitable circumstances. The idea was that the most primitive forms of life which evolved on Earth could not have depended on the chance existence of elaborate chemical compounds of the DNA type—still less on the far more elaborate mathematical constructions of J. von Neumann who had shown theoretically that a very complicated machine which copied itself was possible in principle. Instead, one must look for some very simple and primitive self-reproducing mechanism. The model consisted of wooden pieces of two types which, if initially separated, would remain separated from one another when shaken at random on a track. However, if a correctly assembled pair of pieces was inserted into the track, then the random shaking would cause other pairs also to be assembled in the same way as the first pair. The first pair could also be assembled in an alternative arrangement. Then the shaking would, instead, cause other pairs to link together according to this alternative pattern. However, this original model was severely limited in that only two distinct self-replicating configurations could occur. By designing more complicated pieces which now involved moving parts, Penrose was able to extend the number of alternative configurations which would self-replicate, although in the early models this number remained finite (1958¹⁷³; 1959¹⁷⁴). At this stage, in order to increase the number of self-replicating configurations the pieces themselves had to be made correspondingly more complicated. Since these pieces were intended to be analogous to inanimate molecules, this was a serious drawback. For a truer analogy one would require pieces of a fixed degree of complication out of which an infinite variety of self-replicating configurations could be constructed. Penrose was able to achieve this, in effect, by building pieces which could form chains of arbitrary length in one dimension and with a width of two or four pieces in another (1959¹⁷⁷; 1960¹⁸³). Pieces could be added to the sides of these chains until the width was doubled. Then the whole chain would split down the middle and two chains each identical with the original one would result. In this, a certain guidance was supplied by the nature of DNA, in that a 'code' could be built into the chain which would replicate itself. However unlike the pairing of 'opposites' which occurs in DNA, here it proved more convenient for each element of the code to replicate itself directly. These models became very elaborate indeed. A drawback in the analogy was always that the 'molecules' themselves had to be very elaborately and ingeniously designed and some simplification

seemed warranted. A fundamental difficulty with these self-replicating chains had always been how the daughter chain could tell that it was to separate from the parent *only* when it had achieved a length equal to that of the parent. It had seemed possible to arrange this only with very complicated mechanisms, but then Penrose hit on a 'diagonal link' which solved the problem in a very neat way.

A new piece could be added only at a position matching the lowest unpaired element of the chain but it would *not* link to *that* element, but diagonally to the one just above it. At the same time it would release the diagonal link which had previously existed. In this way the chain being assembled would release from the parent precisely at the point at which it was completed and no sooner.

It seems that Penrose's experience with his self-replicating models had led him to believe that a single-chain replication owing to its more primitive simplicity ought to have played an important role in the early development of life at a time before DNA had established itself. Whatever may be the significance of this particular idea it does seem that Penrose's very individualistic excursions into 'practical self-replication' could, if followed up, provide a totally new approach to the problem of self-replication. It would not be hard to argue that the analogies between chemical bonds and wooden ratchets are totally superficial. Indeed, it is uncertain the extent to which Penrose himself regarded his wooden models as a serious analogy. His sheer enjoyment in constructing such things and in demonstrating them to others would often get the better of him. But the models must undoubtedly have a serious purpose also, and in fact he made attempts to find a chemical analogy which might conceivably also exhibit self-replication in a manner similar to that of his wooden 'diagonal link' model (1960¹⁹¹).

The Kennedy–Galton Centre (1965–72)

On reaching the age of 67 when it was obligatory for him to retire from his University Chair, he did not stop his research work. He simply moved it to a new laboratory. This was called 'The Kennedy–Galton Centre for Mental Deficiency Research and

Diagnosis' and it was opened in 1965 with Penrose as Director. It was located at Harperbury Hospital which is the main mental deficiency residential unit for the County of Middlesex. The name of the new laboratory was chosen to indicate that much of the fund which enabled it to be first established came from the award he had received from the Joseph P. Kennedy, Jr Foundation in 1964; and also to indicate that the scientific standards would continue to be as high as those he had always insisted on at the Galton Laboratory.

Much of the work of the research group he collected round him was concerned with cytogenetic, clinical, and other aspects of mental deficiency (1973²⁹⁵). He directed these activities with enthusiasm and initiated several new approaches. Among these was the study of the formation of dermal ridges in early fetal development using electron microscopy. He also carried out various other investigations into dermatoglyphics.

His earlier work on dermatoglyphics in relation to mongolism has already been discussed. The subsequent emergence of human cytogenetics re-awakened his interest in the subject and in his last years at the Galton Laboratory he had started to investigate the dermatoglyphic anomalies to be observed in the various clinical and developmental abnormalities which could now be precisely defined in terms of the chromosomal findings. Further investigations on mongolism and mosaic mongolism were carried out as well as analysis of the dermatoglyphic patterns in cases of D trisomy (1966²⁴⁰), E trisomy (1969²⁶⁵), polyploidy (1968²⁵³), trisomy 8 (1972²⁸⁵), and also in the various sex chromosome abnormalities. The latter (1967²⁴⁵) produced a quite remarkable result. It was found that the average total ridge count on the fingers progressively decreases with increasing numbers of sex chromosomes. In males the order was found to be $XY > XYY > XXY > XXYY > XXXY > XXXYY > XXXXY$, the effect of an additional X chromosome being about three times as marked as that of an additional Y. In females the order was $XO > XX > XXX \approx XXXX$. This influence of the sex chromosomes on the ridge counts was unexpected because it had previously been shown by determining interfamilial correlations for total ridge count between parents and children and between sibs of the same and different sexes, that the characteristic must in general be determined by genes on autosomal chromosomes.

He had also while still at the Galton Laboratory begun a quite new line of work into the general topology of the systems of dermal ridges and he developed this further in his final years at Harper-

bury. The ridges which make up the dermatoglyphic pattern on the hands and feet are parallel in small fields, but they gradually curve and so give rise to complex patterns. There are two main kinds of discontinuity. These are called loops and triradii. A loop is formed when the direction of a ridge field turns through 180° . A triradius occurs when three ridge fields meet. Penrose's studies on dermatoglyphic topology were first directed towards elucidating the relationships of these two sorts of discontinuity in determining the overall pattern (1965^{232, 236}). From a consideration of the patterns he derived the general formula $T + 1 = L + D$, where T is the number of triradii on a palm or sole, L the number of loops, and D the number of digits. Thus for the normal hand with five digits, the number of triradii exceeds the number of loops by four. This general rule was found to hold for any limb deformity originating in early life such as polydactyly, syndactyly, and ectrodactyly. A number of other general topological characteristics of the ridge patterns were also worked out.

Following this approach the idea was to devise a new method for classifying the overall patterns on the hands and feet in terms of the loops and triradii which were present; the loops for example being specified according to the particular configurational areas in which they occurred and the direction of their cores. This general method of topological classification was first worked out for normal palms and soles (1969²⁶⁹; 1970^{276, 277}). It was then applied to the dermatoglyphic patterns observed in various chromosomal abnormalities such as mongolism, the D and E trisomies, and the 'cri du chat' syndrome; and discriminant functions were calculated which gave the optimal differentiation between the various abnormalities and the normal (1971²⁷⁹). It was shown that the method could be of value in arriving at a correct clinical diagnosis. In view, however, of the availability of reliable cytogenetic procedures for reaching the diagnosis in these particular abnormalities the method was likely to be of only very limited practical value in these disorders. However, Penrose believed that an extension of this general approach to the study of mosaicism particularly for chromosome No. 21 might prove to be of considerable practical importance, because here cytogenetic diagnosis by standard procedures presents considerable difficulties and is much less secure. It was on this problem that he was working when he died.

Other Interests

Apart from his scientific work he had a variety of

other interests, though it was always difficult to see how he found time for them.

In his early days he had been greatly influenced by Wilfred Trotter's *Instincts of the Herd in Peace and War*, and throughout his life he was interested in group behaviour and the problem as to how this might be studied objectively. Some of his ideas were formulated in a short monograph *On the Objective Study of Crowd Behaviour* (1952¹²³). In the 1930s he was associated with the Psychologists Peace Society whose formation had been stimulated by correspondence between Einstein and Freud on hopes for peace. They held meetings in London to discuss normal and abnormal group behaviour. This organization like many others was overwhelmed by the outbreak of the 1939–45 war. However, in 1951 when the Korean conflict looked like developing into yet a third world war, a letter to *The Lancet* signed by Penrose and others led to the formation of the 'Medical Association for the Prevention of War'. Apart from the study of war and its causes, the organization was concerned about the dangers arising from radiation and with medical ethics in relation to war and its preparation. In 1961 he played an important part in starting a series of annual conferences under the auspices of the association, which became a wide ranging forum for discussion of war and its prevention, by people from many different fields besides medicine. He was chairman of the Association for more than 10 years.

He was always a great enthusiast for chess. While still at school (circa 1908) he had for some reason sent a problem to an Australian newspaper and was delighted by the headline 'Hats off to wizard Penrose'. At Cambridge he obtained his half-blue for chess and throughout his life enjoyed playing the game and following the championship matches and international tournaments. As a young man he had established a reputation as a chess problemist specializing, most appropriately for a future geneticist, in that variety known as 'mutate'.

Another interest was the 'Shakespearean Authorship Society'. It used to amuse him to call it the anti-Shakespeare society, but he nevertheless took it quite seriously. His favourite candidate was probably Edward de Vere, 17th Earl of Oxford. But he was always very careful not to commit himself. He lectured to the Society on three occasions; in 1959 on 'Statistical approaches to the authorship problem', in 1961 on 'The Shakespeare portraits', and in 1964 on 'Shakespeare's knowledge of medicine'.

As a person he was diffident and unassuming and often appeared withdrawn and abstracted. But he had a keen sense of the ridiculous and a subtle

humour. He could be a delightful companion and was also generous in his help and assistance to young research workers and many others who came to him with their problems. However, he could not abide anything which he regarded as pretentious or showy and some people in consequence found him a very prickly customer when they came to enlist his support. He also knew how to be 'difficult' in committee if things were moving in a direction of which he did not approve. Penrose and his wife, Margaret, were always extremely hospitable and they appeared constantly to have people from all over the world to stay with them—students, distinguished scientists, and many with quite other interests. They were always particularly kind and generous to those who had come to England as refugees. Penrose especially delighted in having visitors stay at his beautiful Tudor country house at Thorington in Suffolk, which he had acquired in the 1930s and had characteristically donated to the National Trust.

Anita Lax has kindly given her permission to include, in a slightly abbreviated form, a delightful essay which gives an account of Penrose in his home setting. She with her parents and sister, had stayed with the Penroses when they first left Czechoslovakia at the time of the Russian occupation in 1968. A few years later when she was 15 years old she had to write an essay in preparation for her school certificate examination. The subject was 'An interesting character' and she chose to write about Penrose. Anyone who knew him will immediately recognize it as an authentic portrait. It is a fitting way to conclude this memoir.

An Interesting Character

By Anita Lax

He was an old professor of genetics (human genetics) but he may just as well have been a professor of almost anything under the sun, beginning with music, mathematics, chess, art and ending with woodwork. He used to invent ingenious puzzles for his innumerable grandchildren and then he would make them from wood in his little workshop, always considering carefully the ages of 'all these little boys', which, as he said laughingly, changed every year and you had to be careful to keep track of them!

He lived in a tremendously large, old and extremely cold house, the number of rooms of which he never could remember. His equally absent-minded and exceptionally kind wife would continuously have several foreign students and other visitors staying (simply because 'they had nowhere else to go') but neither she nor the professor were

ever quite sure who they were or whether they hadn't already left.

One of the rooms, however, was the professor's study, where, among the pictures, self-reproducing machines, puzzles and books, many of which he had written himself, there was a small, 18th century spinnett on which he loved to play. While you were listening, he would give you one of his ingenious puzzles 'to keep you amused'. If you managed to solve it (and what he never realized in his charming modesty was, that not everyone was endowed by a mind as great as his), his blue, deep-set eyes would twinkle behind his spectacles, and he would run off to bring you a new, slightly more difficult one, laughing in his very characteristic way. He found everything amusing, even the most difficult (or possibly particularly the most difficult) mathematical or scientific problem.

During their free weekends—and there were not many of these, because they were always organizing doctor's meetings for the prevention of war, if not chess matches or amateur orchestras—he and his wife would go to Thorington where they had a beautiful old 16th century home. On the way they would probably spend two hours on the road repairing the almost also 16th century car which very rarely reached any place without breaking down. (There was never any time to buy a new one—too many more useful things to do.)

Once at Thorington, the professor would settle down among the trees of the mysterious and beautiful old garden (he was always amused by the one with the roots growing upwards), equipped with crayons and sketching pad and would draw the most detailed and meticulous sketch of a plant or landscape. He always saw more in everything than everybody else did—by simply observing. His power of observation was one of his most prominent characteristics—whether it applied to his patients, colleagues, or the kite he happened to be flying with the children.

Then he would sit on a bench, in the same old brown-grey, worn little jacket which he always seemed to be wearing, wherever he was, in his black down-at-the-heel shoes, pull out a little notebook with a coloured cover, and start calculating and proving a recent mathematical law or working out a chess problem, or even inventing new games and 'machines' for his mongol patients of whom he was so fond.

I am indebted to Margaret Penrose and Helen Lang Brown for much valuable help and information; to Cedric A. B. Smith, Roger Penrose, and Anita Lax for their separate contributions; and to Jean Edmiston for her assistance with the bibliography.

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