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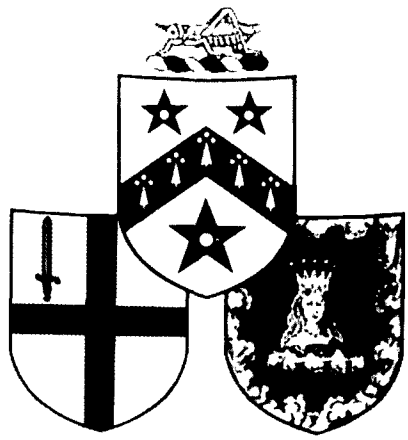


GENETICS, EVOLUTION AND EUGENICS

Second of Two Lectures by

PROFESSOR HILARY ROSE & PROFESSOR STEVEN ROSE
Gresham Professors of Physic

6 December 1999

The Unhappy Marriage of Genetics and Eugenics to the Not so Natural History of the Gene

This lecture will be split down the middle. First I shall pick up the account of the unhappy marriage between genetics and eugenics and their close kin with evolutionary theory, which we covered for the 19th century in the last lecture. Today I take the story into the twentieth. It has only been in our century that eugenics turns from ideas into widespread public policy. Then Steven will take the central concept of the gene and by retracing its history from 1860 to 1960, show that, far from being a fixed category what is meant by biologists when they speak of genes has changed over time and how the models of the geneticists have interacted with eugenics.

There are two major gaps in our understanding of what became known as Social Darwinism and evolutionary theory. The first is between the social historians' understanding of Darwin and Darwian theory and the reading preferred by the biologists. The former recognise the social agenda, making the gap betwen Social Darwinism and Darwinism more metaphysical than real. Biologists mostly prefer an account which emphasises fitness as part of biological discourse, thus many progeny and not the reproduction of existing social hierarchy. The second huge gap lies between the popular discussion (and I include many geneticists in this, for being even a brilliant contemporary geneticist does not automatically make one into a historian of eugenics) and the historians' discussion of eugenics. What I aim to do here is to begin closing the gaps. Thus what I call the "eugenics Yuk horror" response - has to be overcome as it gets in the way of understanding. First it inhibits us from interrogating the diverse strands in the history of eugenics , and not least eugenics as integral to the welfare

state - that immense achievement of the twentieth century. Second it prevents us from looking at what this 'new eugenics' might be.

The unhappy marriage

Despite the efforts of historians to distinguish between different ideologies and practices of eugenics, in popular culture and all too frequently in the public discussions of the ethical aspects of the new genetics, eugenics is historically frozen, always to be equated with Nazi eugenics. There is a tremendous resistance to acknowledging, particularly in the UK, the unequivocal recognition by the leading geneticists and molecular biologists who planned the Human Genome Poject during the mid eighties that with the new genetics would come the new eugenics. My hunch concerning the greater willingness of the US to confront the newest phase of the unhappy marriage of genetics and eugenics, is that the US is a much more self confident society, feeling empowered by American Exceptionalism. Half a century after WW2 the UK still seems to be having troubles in settling down to being a middle sized nation without an empire..

Thus in the UK when geneticists talk about eugenics we find that many insist that contemporary genetics has nothing to do with eugenics. Instead they equate eugenics solely with coercive measures by the state. In this model the Nazi laws to outlaw marriage between the fit and the unfit, to compulsorily sterilise Jews, Gypsies and the mentally ill or retarded, before moving onto the final solution, are the template of eugenics. But this position is absurd. It implies that all those who were not in a position to coerce were not eugenicists. So the very definition of what is eugenics excludes the inventor of the concept, Galton, to say nothing of the extraordinary diversity of intellectuals of every political stance, from Shaw, throughthe feminist birth controllers, Harold Laski, Darwins older son Leonard, the Webbs, to the Myrdals etc etc. who were between them all intellectually committed some version of eugenics. In this late nineteenth early twentieth century enthusiasm the only significant group of

intellectuals who were never part of the conventional eugenic wisdom were the Catholics. Eugenics, however much it varies, is always a protestant or secular narrative.

Evolutionary theory and the happy marriage.

Although the history of eugenics is steeped in racism, hatred of the poor, misogyny, and hatred of mentally handicapped people, this is a reflection of the prevailing cultural values of the time. Sympathy for the labouring poor found little support in Victorian Britain. Elizabeth Gaskell was massively criticised for North and South because she showed sympathy for the plight of the poor - and even worse she recognised the legitimacy of their feeling that they needed to defend themselves. For bourgeois Victorian values the poor were poor because they were lazy and only had themselves to blame for their situation. Those who failed to secure employment were put into the workhouse; the destruction of outdoor relief removed the rights of the poor to participate in everyday society. Indeed the new poor law was probably the first UK eugenic policy, for husbands and wives were sexually segrated. Only the dramatically sentimental Dickens found the way to touch the Victorian heart and make it care about at least one child caught in the work house system. (Of course given that Oliver is of good blood so never should have been there in the first place suggests that Gaskell's and Dickens' novels were rightly seen as engaged in very different tasks. Tear jerkers and nuanced social criticism are different).

But eugenic and evolutionary thinking have long been close. It starts of course with the Malthusian roots of Darwin's theory. But within evolutionary theory the problem lies in Darwin's concept of fitness. Fitness is central to evolutionary theory, but he uses the concept in two radically different ways. When he discusses flora and fauna fitness equals reproductive success - many progeny. But when Darwin turns to look at the human population, this concept of fitness radically changes. It is clearly inconceivable for Darwin to suggest that the fecund poor are the fittest. So

he suddenly changes tack: 'fittest' is no longer about many progeny, but is suddenly filled with new social meaning so that the pale Victorian gentleman is at the apex of his kind. The dreadful thought of having to say that the poor are the fittest, which flows like night after day from evolutionary theory, is too much for Darwin. He is much more conventional than the picture of him as the great biologist and theoretical innovator implies. Today Darwin is enjoying such a cult status that it is difficult to recall that Bertrand Russell once described Darwinian theory as a conservative social theory applied to nature.

But if Darwinian theory gave support to Victorian social hierarchies, which introduced ideas of competetion and the struggle for existence into natural selection even while he sought to insulate his science from politics. Thus he was not very enthusiastic about Herbert Spencer's application of natural selection theory to the evolution of human society. Spencer's language of 'Nature red in tooth and claw,' ' the struggle for existence,' ' the survival of the fittest' made Darwin uneasy even though Social Darwinism was a language and a representation of the social world which was wonderfully apposite to the rising bourgoisie of both the UK and America. Spencer (like Darwin) assumed that the poor were the unfit and that the socially successful were the fit. For him Darwinian science (unsurprisingly if we recall its Malthusian roots) revealed that the provision of welfare merely intervened in the great evolutionary process. The unfit should be neglected, evolution should be permitted to take its natural course. Spencer's profound conservatism meant that he singularly failed to recognise that Darwins's mechanism of selection was to provide the theory with an account of change - ie of transmutation over time.

Eugenics and the Welfare States

Eugenics in some form has been a crucial dimension of the formation of the welfare states. The idea of wanting a well born population is after all so vague and benign that providing we supresss the trained-in yuk horror response, almost anyone can sign up to it. Certainly the variety of

scientific theories underpinning a commitment to the broad church of eugenics was considerable. Galton's biometrics and his belief that heredity was 'in the blood' differed from Lamarckian and Mendelian models of genetics but underneath all the many versions lies the concept of population. Thinking about the people who lived in particular countries or regions as populations only came into cultural existence in the eighteenth century. Population is central to that discourse - most powerfully developed in Scotland- of the bills of mortality and morbidity. This was the birth of what we now speak of as social statististics. It is worth remembering the 'state' part of statistics, for those numerical indicators of health and economic conditions were seen as figures of importance to the state.

Thus thinking about the idea of the eugenic or wellborn human population is in terms of policies which inhibit the reproduction of the unfit (negative eugenics) and encourage the fit to reproduce in number (positive eugenics). This sounds as if we should compare the well being of a human population with say the improvements acheived by Turnip Townsend and the other plant and animal breeders of the 18th century. But their remarkable achievements were achieved through practical agricultural experiment by selection*and* good husbandry. With plants and domestic animals this was easy.

Indeed the eugenics movement of the late nineteenth and the twentieth century echo this. In this multistranded movement some emphasied both selection and good husbandry (and indeed insisted on the role of education as a third as well-informed citizens will act wisely) while the mainstream prioritised heredity to the exclusion of the environment.
In the good husbandry mode we have Disraeli proposing the Public Health Act of 1875
'...the public health is the foundation on which repose the happiness of the people and the power of a country. The care of the public health is the first duty of a statesman'

Disraeli's One Nation conservatism fits neatly into the good husbandry version of securing the well born population. The whole Victorian era is thus a huge struggle within the bourgoisie between the do nothing laissez faireists influenced by Malthus, Darwin and Spencer and the interventionists such as Disraeli who see that the care of the whole nation potentially strengthens the nation.

Nonetheless by the fin de siecle the belief that heredity was all and that only eugenic action - both positive and negative - could lift the race, was part of the conventional wisdom of the age. As we suggested last time the diversity of the supporters was immense. Thus Shaw's Man and Superman celebrates eugenics and sexual liberation. For him only when women and men are free to choose their sexual partners (unconfined by ideas about a good marriage) can they make the best eugenic choices. The Shaw joke about the actress desirous making the perfect baby remains. Sexual liberation was no part of the agenda of the social conservative eugenicists: their preoccupation with eugenics much more reflected their fear and loathing of the social failures. These - then and now - were distinguished from the respectable working poor by terms such as the social residuum, the dangerous classes, the lumpenproletariat and today by the underclass.

State eugenics

A number of historians, although perhaps Diane Paul says it most plainly, suspect that this multi-stranded eugenic enthusiasm was only turned into public policy because of the Great Crash of 1929. Millions were thrown out of work. How was the state to rebuild economy and society from the wreckage? Malthus over a hundred years before had argued that the surplus should be sent to the colonies and in the terible years of the 1830s some 400, 000 a year were leaving Britain alone. Suddenly the idea of a surplus population was on the agenda again but this time mixed up with the new ideas about the quality of the population.

If we now turn to the concrete world of state eugenics, away from the intellectual debates and into practice we see that the compulsory sterilisation of feebleminded or morally lacking women was a standard pre Nazi feature in the formation of the Protestant welfare states. The US despite the white Protestant ascendancy, as usual followed no consistent federal policy, but California sterilised with energy. There were curious exceptions such as Britain and Holland who adopted segregated institutions as a non violent strategy leaving sterilisation as a voluntary option.

As we have argued, genetics and eugenics have had a constantly troubled relationship. Thus genetics which had begun by sharing the widespread cultural belief that feeble mindedness was heritable, produced powerful research by the fifties, demonstrating that this was not the case - above all in the case of Downs Syndrome. But such advances in genetics did not open the doors of the sexually segregated institutions caring for the mentally handicapped in the UK, nor stop the sterilisation in the Scandinavian Welfare States. These latter merely changed their argument . Now they took the view that feeble minded women were not equipped to bring up normal children so still sustained a sterilisation policy but without the aid of genetics. It is dificult to interpret this except as the state's coercive control over women determining who is fit to mother. The possibility that women who are seriously learning disabled will feel they have enough to do caring for themselves and that often with help, so will not want the reponsibility of a baby is not to be risked. In a statist society the state takes those decisions.

Industrialised countries might have shared the Crash but they started in different places. The settlement of 1914-18 had cruelly beggared Germany, there even before the Crash the task of rebuilding the society was probably the most acute within Europe. Such conditions made fertile ground for Hitler's social vision - though we would probably want to say nightmare The US was as always complicated, not least because of its federal structure.

Individual states pioneered compulsory sterilisation in the frist years of the century. What checks were made on this were less as a result of geneticists concerns about the questionable science claimed to support the policy, than though legal challenge. US practice was constantly held up by the eugenicist theorists in Germany as the way to go. German and later Nazi geneticists collaborated enthusiastically with their US eugenicist counterparts.

Nowhere (other than the catholic countries) was free from eugenic enthusiams. Indeed the German state with its Northern Protestants and its Southern Catholics did little about eugenics until the advent of the Nazis. In such a divided religious context the doubts of numbers of geneticists received a hearing. The new Soviet Union was experiencing terrible difficulties, the revolution was not deepening and democratising society - instead Stalin had seized power. Britain after a flurry of reform immediately after 1914-18 was not an energetically reforming state during the interwar period. It took the second WW to provide the context for Beveridge and the development of the British version of the Welfare State. During the interwar period (and the Swedes were neutral so they had a littlr more space) Swedish Social Democratic theorists fought for a middle way between Market capitalism and the Soviet model.

Marquis transparency

For the Myrdals - the great theorists of the Scandinavian Welfare State- eugenics was a crucial tool for building the new welfare society. In a poor chiefly agricultural country with huge social ambitions and a strong sense of collectivity - remember this was the time of a huge well organised labour movement - their proposals made sense. Sweden like the other Nordic countries is deeply Lutheran and so shared a very strong version of Protestantism in which duty (not individual rights) are very much to the fore. Culturally Scandinavia is closely linked to Germany, so strong eugenic and nationalistic social ideas moved freely between them. The

crucial differnce was that the Scandinavians never tied their eugenic policy to anti- semitism and racism - inded they actively denounced the Nazis on this- nor did they move to kill their mental patients.

Myrdal transparency

Steincke transparency

But what was being said in Germany was not too different

Hitler transparency

Mixed Transparencies of Swedish, Norwegian sterilisation etc

Eugenics Today

The end of the long post war boom, the weakening of collectivism and the retreat of the welfare state, the reductionism triumph of DNA, the recognition of the new biotech market are fragments from the story of the move from a collectivism and state eugenics to individualism and consumer eugenics. We find parents asking that their near adult disabled daughters are sterilised, and while it is not difficult to understand their position there is an absence of ethical public discussion The problem, rather being faced by society, is left to be carried by the already over burdened parents, for it takes place in a society not conspicous for its sensitiveity to people with special needs. But even if the core change as that to consumer eugenics, context is still crucial. The dystopia of Gattaca could only be arrived at in the context of an unregulated biomedical market and the total commodification of reproduction (as for example proposed by Lee Silver in Remaking Eden) is not imposed by the state. Meanwhile as European social capitalism and biotech are a good deal more regulated than that of the US (e.g. Germline therapy and human cloning are illegal throughout the EU and not illegal in the US), the US is much more immediately at risk from the Gattaca scenario than Europe However we need to remind ourselves that Prime Minister Blair like his predecessor seeks to row us across the Atlantic.

Thus even though the ideology of informed choice, backed up by the material and proliferating powers of the DNA tests, today place huge

burdens on the individual and their family, not least the individual pregnant woman, the contexts within which this choice is made are significantly varied. As we will discuss in the next lecture, the very different regulatory regimes are themselves under under continuous pressure not least because the pace of innovation is tremendous and the financial stakes high.

K.K. Steincke - the architect of the Danish Welfare State

1920 The Welfare System of the Future.

In this Steinke fuses social welfare provision with robust eugenic policies "to improve the race"

Gunnar Myrdal
1941

our day of highly accelerated social reforms the need for sterilization on social
ounds gains new momentum. Generous social reforms may facilitate home-mak-
g and childbearing more than before among the groups of less desirable as well as
ore desirable parents. This may not be regretted in itself as the personal happi-
ess of these individuals and the profitable rearing of those of their children
teady born are not to be neglected. But the fact that community aid is accompa-
ied by increased fertility in some groups hereditarily defective or in other respects
eficient and also the fact that infant mortality among the deficient is decreasing
emands some corresponding corrective.[47]

(The state) must see to it that only the healthy beget children; but there is only one disgrace: despite one's own sicknesses and deficiencies, to bring children into the world, and ones highest duty is to renounce doing so.....(The state) must put the most modern medical means in the service of this knowledge. It must declare unfit for propagation all who are in any way visibly sick or who have inherited a disease .

Adolf Hitler Mein Kampf

REPORTED STERILIZATIONS IN SWEDEN 1935-75

YEAR	AVERAGE ANNUAL	%WOMEN
1935- 1939	383	93%
1940-45	1,450	70%
1946	1,847	DK
1947-56	2,082	93%
1957-66	1,557	97%
1967-75	1,548	99%

TOTAL 1935-75 62,888 % women 93%

(Peak year 1949: 2,351)

Source: Broberg and Tydén from Swedish Central Bureau Statistics

STERILISATION IN DENMARK 1935-50

	women	men	total
1935-75	88 (81%)	20	108
1935-39	975 (71%)	405	1,380
1940-45	1,510 (71%)	610	2,120
1946-50	1,771 (76%)	561	2,332

Sterilisations in Norway 1934- 76

	Sterilisations	Per cent Women	Annual Av.
mid 1934- end 1942	653	83	76
1943- may 8 1945 (Nazi law)	487	84	207
may 9 1945-june 54	2,569	91	283
july 1954-1965	8,005	93	696
1966-76	29,177	62	2,652
1934-76	40,891	75	951

A Century in The History of The Gene

1860s	Mendel	Hidden Determinants
1900	Weismann	Immortal germplasm -one way flow of information
1910-30	Morgan	Genes mapped on chromosomes
1920s	Muller	Mutations to order "genetic load"
1940	Beadle/Tatum	One gene = one enzyme
1940-53	Crick/Watson	Genes are lengths of DNA
1960s	Crick	The Central Dogma: "DNA makes RNA makes protein"

one way flow of information

"Once information has got into the protein it can't get out again"

Gresham lecture 3 – part 2

What is a gene? An unnatural history

Everyone knows what a gene is – a length of DNA that codes for a protein, and that in some way 'determines' some aspect of an organism, eye colour, likelihood of suffering from Huntington's disease, or whatever.

Well that's what today's view of genes is – or rather the view you might get from all those newspaper headlines we discussed in the first lecture. The problem is first that that simple view, which might have been held twenty years ago, is no longer quite so straightforward. And second, that arriving even at that view of the gene has been far from 'natural.' In fact the idea of what a gene is has changed profoundly in the last hundred years.

The last lecture discussed the birth of genetics, and counterposed the work of Mendel and Galton. Mendel, working with peas, had come to the conclusion that inside each organism there were 'hidden determinants' – units that could be transmitted from generation to generation, without mixing, and carried in some way what we would now call instructions – to make green or yellow, wrinkled or smooth peas, or whatever. Galton measuring a whole range of traits in humans from height to handgrip found that these variables were not discontinuous, either/or like Mendel's peas, but seemingly continuous, and that heredity in some sense blended, so that a person's height reflected the mean of his or her parents' height, for instance. We also saw how, this blending inheritance was a huge problem for Darwinian evolutionary theory, as it would mean that any favourable variation would quickly get diluted out in the population. This difficulty, which Darwin could never solve, meant that by the end of the 19th century his mechanism for evolution- natural selection – fell from scientific favour.

The story we have to tell this time is that of how, over the course of the 20th century, Darwin, Mendel and Galton came to be reconciled in what has become known as the modern synthesis. None of them were much concerned with what

became the major task of the next century, determining the physiological basis of inheritance and selection. By the end of the 19th century, with the more powerful microscopes that were then available it became possible to begin to look at the structure of individual cells and their components.

Transparency of cell, plus nucleus etc

When the microscopists looked at cells that were in the process of division, they found that within the nucleus there were strange ribbon like structures that could be stained with special dyes – they called them chromosomes. Chemically, it was relatively early established that chromosomes are tight bundles of proteins wrapped around the nucleic acid DNA, although the significance of this was not to become clear until the 1950s.

Transparency of chromosomes

Working with a tiny threadworm, *Ascaris*, physiologist August Weismann, in Germany in the 1880s observed that each body cell had two large chromosomes, whilst its sperm and egg cells only had one each. When Ascaris reproduced, sperm and egg fused, and the resulting cell and all its daughters had two chromosomes once more. Weismann argued that the chromosomes represented the actual physical units of hereditary transmission. He called them the germplasm. Germplasm, he felt, was immortal. In an attempt to contrast Lamarckian with Darwinian ideas of evolution, he cut off the tails successively of forty generations of mice, without making any difference to the length of tails of their offspring. Hence germplasm could not be affected by the life events in any individual but was passed on unchanged from parent to offspring. This barrier to the inheritance of acquired characteristics became known as Weismann's barrier, and endowed his germplasm with almost mystic significance – the forerunner of today's holy grail of DNA. Of course it wasn't a real test of Lamarckism – after all mice don't strive to have their tails cut off. And even though I was born into a

Jewish family, I still had my foreskin at birth despite the fact that generations of my antecedent males – according to the family narrative – had been circumcised!

Rediscovering Mendel

So when after a forty year gap Mendel's work was rediscovered in 1900, it could be argued that his hidden determinants were in fact in some way physically located on the chromosomes. The hidden determinants became genes, and genes, one of Mendel's rediscoverers, Carl Correns, argued, lay along chromosomes. Mendelian ratios began to be collected in many species, even in humans – for instance for eye-colour, or colour –blindness.

What is more, a number of the early geneticists (the term was invented by William Bateson, in Cambridge and the concept of gene by Johannsen) went on to argue that changes in the structure of the chromosomes – *mutations* - could result in large changes in the phenotype of the organism, or *sports*. Hugo de Vries in particular found many such sports when he bred evening primrose plants. Darwin had insisted on gradualism in evolution, that nature didn't make leaps. Galton and Huxley had felt that this was a fatal flaw in the Darwinian mechanism, and their successors leaped to the conclusion that de Vries's mutations provided the mechanism that natural selection of small variations could not. This Mendelian idea, that characters were produced by specific genes which could be altered by mutations, lay at the heart of one strand of the eugenic thinking which Hilary discussed.

However, the genetic community was still bitterly divided. Galton's successors, notably Karl Pearson, who occupied the first Galton chair of eugenics at University College here in London, still argued that Mendelian mechanisms could not account for continuous variation, and they developed increasingly sophisticated statistical methods to account for such variation. Instead of considering *individuals*, as the Mendelians did, Pearson and his followers therefore concentrated on populations. They argued that by using statistical methods to study the distribution of a trait in a population, they could calculate a figure that became known as *heritability* that is the proportion of the variance

of the trait in the population that could be attributed to genes as opposed to environment. It is this concept that still today is beloved of psychometricians and behaviour geneticists, when they talk of the heritability of, say IQ, or neuroticism or whatever.

Transparency of heritability

This conflict between thinking of individuals and their Mendelian genes and population thinking still haunts much of today's debate – indeed we saw it only last week in a confrontation over the nature of intelligence and its variation in the population between psychometricians like Robert Plomin interested in individual differences and evolutionary psychologists, interested in human universals presumably evolved through natural selection.

The Modern Synthesis

The conflict between Mendelians and advocates of continuous variation raged on through the 1920s. Eventually both sides had to give ground. De Vries's sports turned out to be something of a special case that couldn't give rise to new species, so Mendelism as a simple motor of evolution could not be sufficient. On the other hand the advocates of continuous variation had to concede that their findings could be explained reasonably simply if instead of there being simply one gene associated with each character, there were many. If for instance a person's height was influenced by perhaps 50 different genes – to say nothing of course of the environment – then this would give the appearance of a continuous, bell-curve like distribution in the population.

The 1930s saw what many regarded as the final 'modern synthesis' of Mendel and Darwin. Small random changes in genes, through whatever mechanism, would be preserved, even though the owner of those genes bred with a partner who didn't possess them, and so would not simply be blended out of what became known as the population's 'gene pool.' Hence, Ronald Fisher and JBS Haldane argued, natural selection could act, and there was a real motor for evolutionary change. For Fisher and Haldane, natural selection acted separately

on individual genes, each of which behaved independently without regard to any other of the genes in the genome. This was rather derogatorily called bean-bag genetics by the other leading population geneticists of the time, the Harvard based Sewall Wright, who insisted that one could not consider genes in isolation but had to think of any individual gene in the context of all the others with which it interacted. In any event, this new genetics made a nonsense of the older eugenicist claims that moral turpitude, not to say poverty, were present as simple Mendelian characters in the genes. Eugenics had to think instead of improving not individuals, but populations. These fights are still with us.

However, for most of these early geneticists, just as is still the case today for theoreticians like Richard Dawkins, 'genes' were not regarded as physical, chemical or biologically 'real' objects. William Bateson, for instance, to the end of his life opposed the idea that genes might have some chemical identity. Rather 'genes' were abstract accounting units, to be fitted into mathematical equations, units that increased or decreased the fitness of the individual within the population – fitness now being defined in terms of the number of offspring the individual parented to survive and breed in their turn. Thus the modern synthesis defined evolutionary change not in terms of changes in obervable phenotypic features such as the length of beak of Darwin's finches, or whatever, but in terms of changes in gene frequency in a population.

Turning Accounting Units into Chemicals

In another part of the forest so to speak, other developments were taking place that were to change all this. The story here moves to the US and a researcher interested, not in genetics, but in development, the processes by which the fertilised egg divides and multiplies over and over in the process of becoming an adult differentiated individual. There are two key figures. One is a human, Thomas Morgan. The second an animal, the famous fruit fly, Drosophila. Morgan's problem was to find the right organism in which to study development. Fruit flies, which bred fast, fed on rotting bananas and could be kept in their myriads in the lab in old milk bottles, proved ideal. Furthermore, they had giant chromosomes which could be easily observed down the

microscope. The chromosomes turned out to be striped, each with a characteristic pattern of bands along its length.

Transparency

Amongst the thousands of fruit flies that Morgan and his students observed, they occasionally found a mutant, one for example with white rather than red eyes or a different pattern of veins on the wings. These characters once they appeared, were transmitted in a Mendelian manner. His colleague Herman Muller in the 1920s found that the rate of mutation could be greatly speeded up by exposing the flies to X-rays or to certain chemicals. Muller noted that almost all mutations were deleterious, and pointed out that humans were constantly being bombarded with radiation which would result in mutations. He rather gloomily concluded that the population carried an increasing genetic load, and that only a programme of positive eugenics would save us from inevitable decline. The atomic explosions at Hiroshima and Nagasaki released huge amounts of mutagenic radiation, and Muller was amongst those calling attention to their long-term genetic effects. These issues too persist today, even though Muller's concept of genetic load is no longer taken very seriously.

Coming back to the Drosophila mutants and the 1920s, cross-breeding them and relating the pattern of mutations carried by the offspring with the chromosomal pattern of bands – I don't want to get into the technicalities here – led Morgan to realise that not only did genes lie on chromosomes, but each had a physical location along them – a map reference so to speak. A new research field, of cytogenetics – the cellular and microscopic study of genes – had been created. The papers this past week have been full of wonder at the publication of the first DNA sequence for an individual human chromosome, chromosome 22, a direct legacy of Morgan's work.

Transparency

So by the 1930s the term gene had two separate meanings. For evolutionists and population biologists it was an abstract accounting unit of fitness. For cytogeneticists it was a map reference on a chromosome. The next step was to give these map references a chemical identity. Drosophila was absolutely not the right organism to do this. Something simpler was needed, and in the 1930s two American microbiologists, George Beadle and Edward Tatum came up with it in the form of the simple bread mould, *Neurospora Crassa.* The mould can be grown on jelly (Agar) in little glass saucers (Petri dishes), provided it is fed simple food, and, just as with Drosophila, one can make experimental mutants. Some of the mutants wouldn't thrive on their normal simple diet; they had to be fed very specific and more complex foods, such as particular amino acids. The mutants lacked the enzymes necessary to convert the original raw diet into the amino acids needed for growth. Complex crossing experiments allowed Beadle and Tatum to make their famous generalisation:

1 gene = 1 enzyme

So were the genes actually enzymes themselves? No-one was quite sure. Enzymes are proteins, and through most of the 1930s and 1940s it was assumed that if genes weren't themselves enzymes, then at the very least they were complex protein molecules. It was work on bacteria that was to provide the next step forward, carried out not by a scientist but by a medical officer in London, Frederick Griffith. He was trying to produce an immune serum for pneumonia. Among several types of pneumococcus, Griffith observed two, called S (smooth) and R (rough). The S form was virulent, the R form was not, and when grown on a saucer they could interconvert, apparently by mutation. In 1928 Griffith perfomed the improbable experiment of injecting living R non-virulent cells into mice along with dead S cells. The mice became infected and colonies of S cells could be isolated from their blood. Hence there must have been some factor in the dead S cells that changed the type of the R cells. What was responsible for the transformation? It had to be a substance destroyed by heating, and in 1933 it was shown to be a combination of protein and nucleic acid. This so-called transforming principle was a bundle of genes. But was it the protein or the

nucleic acid? It took until 1944 when Avery Macleod and McCartney, at the Rockefeller in New York, were able to strip away step by step all the protein and leave the seemingly naked nucleic acid and show that this could still carry out the transformation.

So, genes were made of nucleic acid? Still people found it hard to believe. DNA seemed a rather simple boring, relatively inert molecule, a repetitive structure made up of just four elements, the so-called bases – adenine, cytosine, guanine and thymidine:A,C,G,T. How could such a molecule carry within it all the complexity of a gene, apparently able to turn a non-virulent bacterium into a virulent one, quite apart from all the other things genes were supposed to be able to do.

As everyone knows, the answer came, not from geneticists nor yet biochemists, but from two outsiders, an engineer turned structural biologist, Francis Crick, and the young biologist James Watson, in the biophysics laboratory in Cambridge. It was they, on the basis as we know of data semi-stolen from Rosalind Franklin, who finally solved the puzzle, when in 1953, they produced a structural model of DNA which immediately seemed to solve the problem of how the molecule could generate copies of itself, and in so doing transmit genetic information from one cell to its daughter or one generation to the next.

Transparencies.

That's why Crick and Watson were able to conclude their famous Nature paper with the words

Transparency
"It has not escaped our attention....."

So, in just less than a century, genes had moved from hidden determinants, via abstract accounting units, to map references along a chromosome, to a chemical, DNA.

It remained of course, to show how 'information' embedded with the sequence of ACGT in the DNA could be used to synthesize proteins with defined and complex structures and how these proteins in their turn were involved in generating the complex properties of living organisms that we call phenotypes.

Francis Crick had no doubts. Lengths of DNA formed 'the genetic code.' In order to make proteins, copies of DNA were made onto a slightly different nucleic acid – RNA, a process called transcription. In turn RNA in a manner which was not to be solved biochemically until the 1960s and 1970s, directed the synthesis of proteins.

"DNA makes RNA makes protein" was the formula, and this one-directional flow of information was crystallized by Crick into what he called the Central Dogma of the new molecular biology and genetics.

"once information gets into the protein it can't get out again."

So, DNA is indeed the book of life, the code of codes, just as the headlines and book titles put it?

It will take us our next lecture to show just how mistaken these views are, and to see how yet again in the decades since the 1970s, the idea of what constitutes a gene has been transformed.

may not be too vital. By contrast the protein chain is made of twenty different sorts of amino acid joined head to tail in a unique and non-repetitive sequence. Each amino acid has its predetermined place in the sequence, and altering it in some way, by the replacing of one amino acid by another, or by the inverting of the order of two or more along the chain length, may mean that the protein will no longer fulfil its physiological function within the cell (see, for example, page 39). The protein synthesis problem is one of specificity.

The problem, as it might have appeared about 1950, say, can thus be summarized as that of how to assemble a series of up to 100 amino acids head to tail along a peptide chain so that the order of the amino acids along the chain could be accurately predetermined and reproduced.

It is possible to visualize two ways of building up such a chain. Either we could start with one amino acid, add a second to it, then a third, a fourth, and so on, until the chain is complete; or, alternatively, we could collect together all the amino acids needed for the chain, and, when they were all assembled, link them almost simultaneously one to another (like doing up a zip-fastener). The second alternative seems an unlikely one, and would not be considered at all were it not that the first leads into a morass of difficulties. Consider a hypothetical example. To join glycine to alanine, we can envisage an enzyme which performs the reaction:
(like the glutathione synthesis described earlier). Now imagine

$$\text{gly} + \text{ala} \longrightarrow \text{gly-ala}$$

a second enzyme to add a third amino acid – say tyrosine:
To add a fourth amino acid we need a third enzyme, and to add

$$\text{gly-ala} + \text{tyr} \longrightarrow \text{gly-ala-tyr}$$

a fifth, a fourth enzyme is required. In general, to build a chain of n amino acids, $(n-1)$ enzymes would be required. But as the protein chain grows in length, so the amount of information that the nth enzyme needs in order to add the $(n+1)$th amino acid also increases. In deciding whether to add serine as the

1 NUCLEUS (*above*). **Nu** – nucleus; er – endoplasmic reticulum; arrow shows pore in nuclear membrane. NUCLEAR MEMBRANE (*below*). Arrows show nuclear pores.

Even when the bacterial cell is dividing (marked C and D in Fig. 5(a)), the stain is unable to resolve any further detail in structure within the stained areas. In contrast, when the cell is dividing, the nucleus and the chromosomes can be seen to take up the stain in preference to their surrounding cytoplasm (see Fig. 5(b)). Further, it can be shown that these chromosomes account for about 99 per cent of the total DNA in the cell.

Figure 5(b) Light micrograph of the root-tip cells of the broad-bean, *Vicia Faber*, showing the location of DNA by a staining technique. (× 1 250)

The chromosomes (or 'coloured bodies') are a distinctive feature of eukaryotic cells but are not found in prokaryotic cells. As we shall be using the terms prokaryotic and eukaryotic intermittently throughout this and other Units, let us take the opportunity here to clarify them.

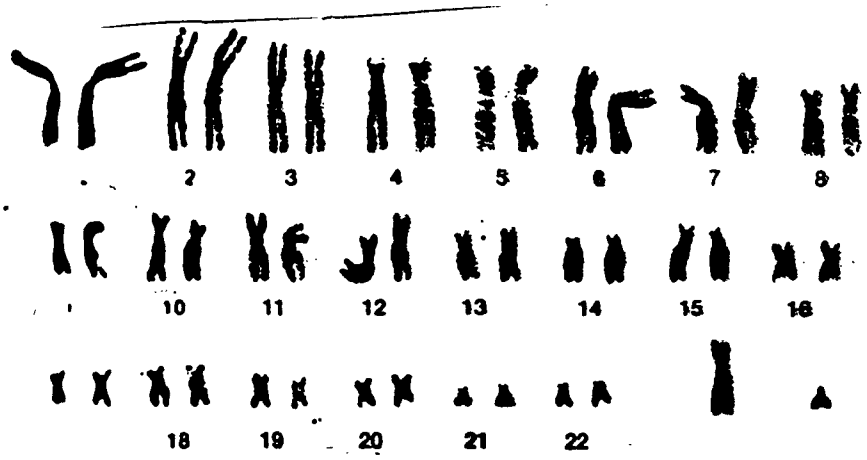
Prokaryotes and eukaryotes

QUESTION Examine the structures labelled N in the electron micrographs (Fig. 6(a), (b) and (c), *overleaf*) and in each case state whether a nuclear membrane is present or not.

ANSWER A nuclear membrane is absent in *E. coli* but present in both the plant and animal cells.

The two 'lighter' areas that seem to contain fine threads in the bacterial cell are not surrounded by a nuclear membrane and do not possess a nucleolus. Such areas in the bacterial cell are referred to as *nucleoids* or *chromatin bodies*, to distinguish them from the nuclei shown in the other two electron micrographs, in which nuclear membranes

nucleoids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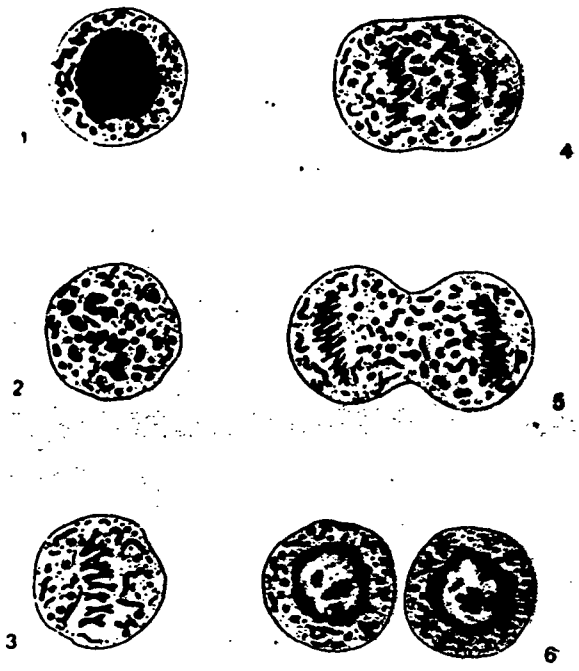
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6

3 Not all members of a family may be available for investigation.

4 As with the German farmer, supposed familial relationships may not always be true.

5 Few such studies have been carried out until recently and, as human generations are long, this means that the inheritance of only a few traits has been studied for more than three or four generations.

All this means that data collection often depends on family records or simple memory—neither very dependable. However, in certain aristocratic families unusual traits (or indeed whims) were noted carefully. The families could afford what doctors there were available; the family chroniclers recorded the information and sometimes from such things as family portraits, the traits are revealed, as in the case of the famous Habsburg lip, which has been recorded in this royal Austrian family over many years (Fig. 2).

Figure 2 The expression of the *Habsburg lip*, over four centuries. (a) Emperor Maximilian I (1449–1519); (b) Emperor Charles V (1500–1558), grandson of (a); (c) Archduke Charles (1771–1847); (d) Archduke Albrecht (1817–1895), son of (c).

In more recent years, it has been possible to construct complete *lineage charts* or *pedigrees* for several families carrying traits. From Figure 3 you can see that *albinism* (a lack of pigment in the skin, hair and eyes) 'runs in families'.

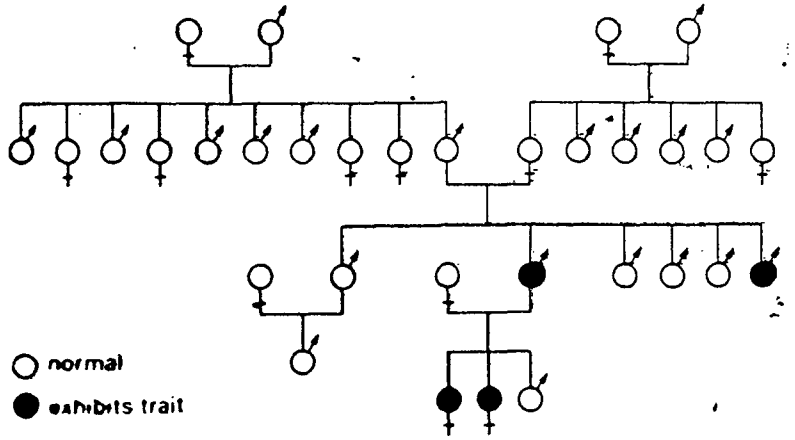
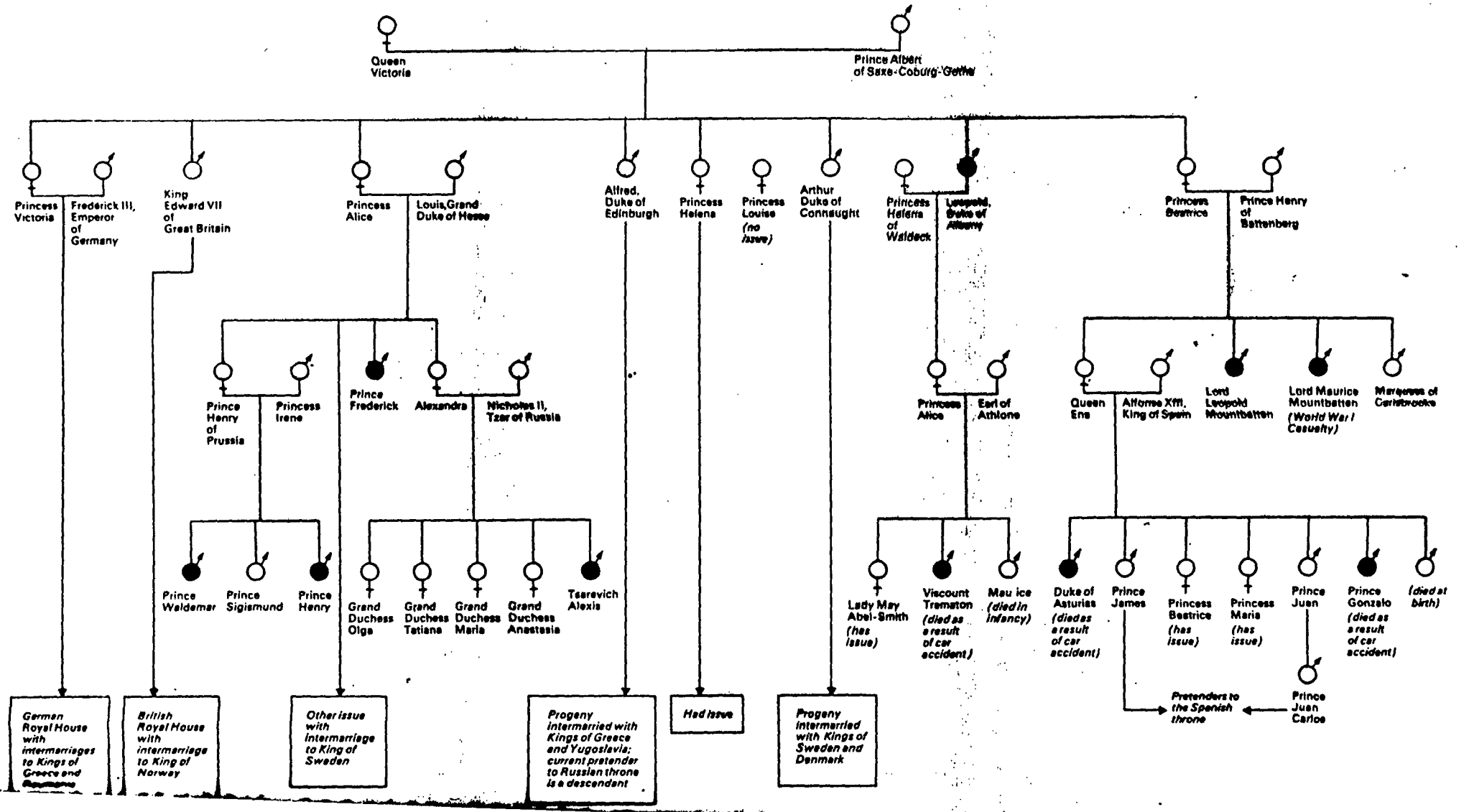


Figure 3 A pedigree chart of a family group in which albinism has occurred.


Queen Victoria
Prince Albert of Saxe-Coburg-Gotha
Princess Victoria
Frederick III, Emperor of Germany
King Edward VII of Great Britain
Princess Alice
Louis, Grand Duke of Hesse
Alfred, Duke of Edinburgh
Princess Helena
Princess Louise (no issue)
Arthur Duke of Connaught
Princess Helena of Waldeck
Leopold, Duke of Albany
Princess Beatrice
Prince Henry of Battenberg
Prince Henry of Prussia
Princess Irene
Prince Frederick
Alexandra
Nicholas II, Tzar of Russia
Princess Alice
Earl of Athlone
Queen Ena
Alfonso XIII, King of Spain
Lord Leopold Mountbatten
Lord Maurice Mountbatten (World War I Casualty)
Marquess of Carisbrooke
Prince Waldemar
Prince Sigismund
Prince Henry
Grand Duchess Olga
Grand Duchess Tatiana
Grand Duchess Maria
Grand Duchess Anastesia
Tsarevich Alexis
Lady May Abel-Smith (has issue)
Viscount Trematon (died as a result of car accident)
Maurice (died in infancy)
Duke of Asturias (died as a result of car accident)
Prince James
Princess Beatrice (has issue)
Princess Maria (has issue)
Prince Juan
Prince Gonzalo (died as a result of car accident)
(died at birth)
Prince Juan Carlos
Pretenders to the Spanish throne
German Royal House with intermarriages to Kings of Greece and Roumania
British Royal House with intermarriage to King of Norway
Other issue with intermarriage to King of Sweden
Progeny intermarried with Kings of Greece and Yugoslavia; current pretender to Russian throne is a descendant
Had issue
Progeny intermarried with Kings of Sweden and Denmark

The Problem of Heritability

The heritability equation

$$V = G + E + (GXE)$$

assumes additivity

only works if GXE is small - i.e virtually no norm of reaction

only meaningful in a specific environment

The Problem of Interaction

..... in general, *m* genotypes in *n* environments, generate (*mn*)!/*m*!*n*! kinds of interaction.

Consider simply 3 genotypes and 3 environments.

Then $mn = 9$

$(mn)! = 9x8x7x6x5x4x3x2x1 = 362,880$

m! and *n*! are each 3x2x1 = 6

Hence no of interactions = 10,080

(JBS Haldane, 1946)

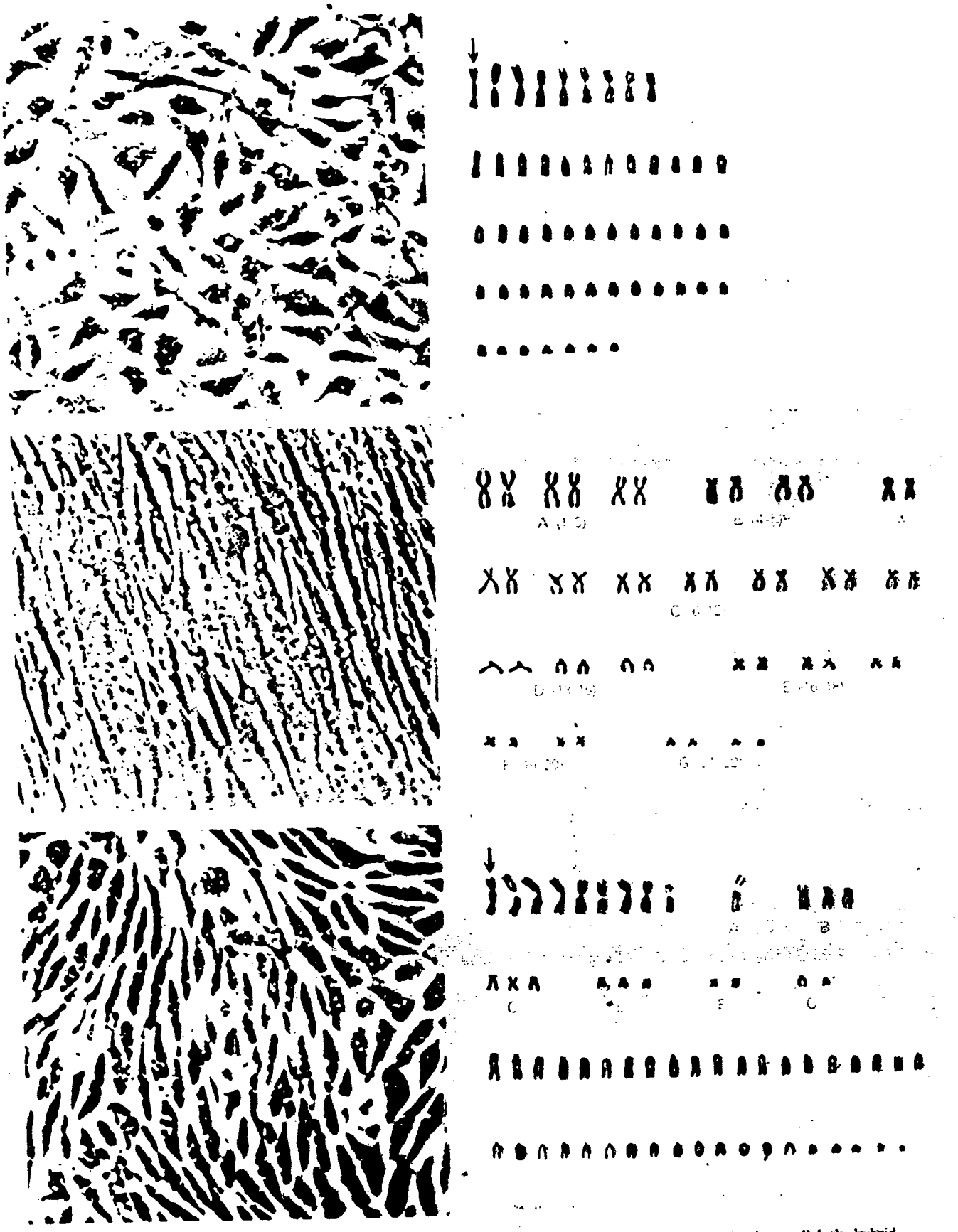


Figure 10 Mouse–human hybrids are illustrated by the cell cultures (*left*) and the karyograms (*right*) of the mouse parent line (*top*), the human parent (*middle*) and the hybrid (*bottom*). The human cells, derived from embryonic lung tissue, contain the normal number of chromosomes (46, or 23 pairs), arranged here in the usual seven groups (plus the two female sex chromosomes). Except for a tendency to align in parallel, the hybrid cells look more like the mouse cells than the human ones. This is in keeping with the fact that the hybrid karyogram contains only 14 of the 16 human chromosomes, which are readily distinguished from mouse chromosomes.

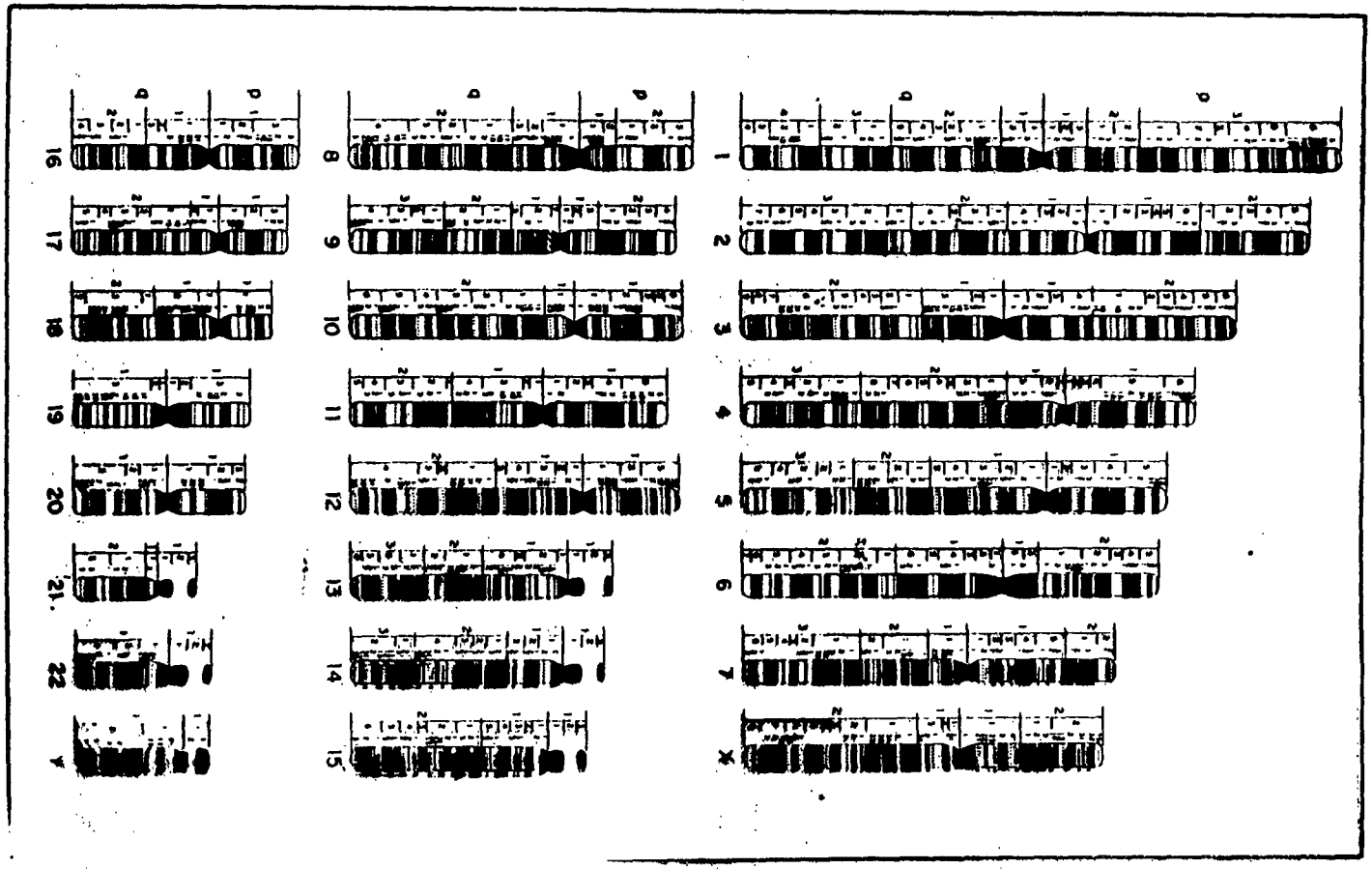
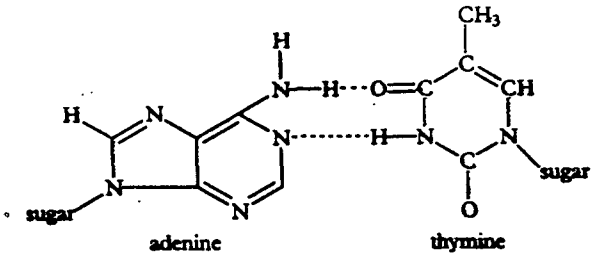
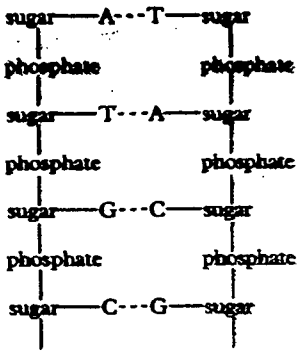


Figure 8

(a) Mortice-and-tenon arrangement of base-pairs.



(b) Bonding of two chains in DNA helix.



(c) Watson–Crick DNA helix

strange tensions that have existed between biochemists and molecular biologists for the getting-on half century since the Watson–Crick discovery can be dated to this episode.

In the structure of DNA shown here, the amount of adenine inevitably equals that of thymine, and guanine that of cytosine, just as the chemical analysis had shown. Despite the restrictions

"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

JD Watson and FHC Crick (1953)

"Molecular Structure of Nucleic Acids"

Nature, v171, pp737-738

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- to foster academic consideration of contemporary problems;

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Gresham College, Barnard's Inn Hall, Holborn, London EC1N 2HH
Tel: 020 7831 0575 Fax: 020 7831 5208
e-mail: enquiries@gresham.ac.uk