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GENETICS IN THE TWENTIETH CENTURY

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This has been a great Congress, with state of the art science and intellectual ferment. All of you in the audience have had the opportunity to share my excitement.

I regret not being here to give my talk at the scheduled time on August 10. Unfortunately my flight was canceled so I arrived a day late. This Congress has therefore had one feature that no other congress has had, having its introductory talk given at the end. I am happy that Dr. Brenner was able to fill in for me on the first day. This is the second time that Sydney and I have been on the same program, and on the earlier program he failed to appear. So there is a certain symmetry in my absence.

I spent a month in China in 1983. How things have changed in those 15 years, in every way, including genetics. At the time I especially treasured the opportunity to visit China's pioneer *Drosophila* geneticist, J. C. Li. Li did important work in the Morgan laboratory in the United States and wrote several papers with C. B. Bridges. He was largely responsible for introducing *Drosophila* research to China. At the time of my visit he was 89 years old, hale and hearty and full of enthusiasm. His physique reflected his earlier career as a football player at Purdue University. Until a few years before, he had bicycled to work and taught genetics courses. I also met C. Y. Zhou, then 81 and a retired professor of agronomy. He was a leading worker in plant genetics, having studied at Cornell with R. A. Emerson. Among American universities, Columbia and Cornell were the two largest influences on early Chinese genetics, which got off to a strong start.

I am particularly delighted to find Li's student and my long time friend, C. C. Tan, on this program. C. C. and I first met at the University of Texas 52 years ago. The story that I heard is that in the early 1930s J. C. Li sent one of Tan's papers to T. H. Morgan, who passed it on to Theodosius Dobzhansky. Tan and Dobzhansky shared an interest in ladybird beetles, and he and Morgan arranged for Tan to come to the United States. C. C. did widely recognized work with Sturtevant and Dobzhansky on analysis of inversions in salivary gland chromosomes and showed the correspondence of homologous gene positions in related species. He also pioneered in transplanting eye-primordia, foreshadowing the later work of Beadle and Ephrussi. At the University of Texas he gave a seminar on mosaic dominance in ladybird beetles, which reminded us drosophilists of the phenotypes at the scute locus. C. C. and I had dinner together in a Chinese restaurant, and he suggested that if he ordered the food we would get more authentic Chinese dishes. Alas, no one in the restaurant could speak Chinese! Between then and now, my life has been easy; his, alas, has not. But I am delighted that a richly deserved honor, the Congress Presidency, has come his way at last. He celebrated his 90th birthday anniversary this week. He has inspired a whole generation of Chinese geneticists.

Genetics is a thriving subject in China, as this Congress has revealed. I trust the Congress will be a stimulus for further work and further international cooperation. When I was here in 1983, Chinese genetics had been through 25 disastrous years. After a strong start in Mendelian genetics from 1920 to 1949, came a period of Lysenko's influence from 1950 to 1957. This was followed by a period from 1958 to 1966 of co-existence of the two genetics, which must have been terribly confusing for students. Then came the cultural revolution from 1967 to 1976. Since 1976 the original genetic program has been gradually restored. It was inspiring in 1983 to see the great zeal and enthusiasm, and especially the ability to do good work without the sophisticated equipment that I was used to seeing at home.

It was a time of optimism, but people and laboratories were poor. For example, researchers had to make their own enzymes and they did not have up-to-date equipment. I was asked by several students to suggest problems that could be done inexpensively. One of my suggestions has borne fruit. I had been interested in "the poor man's genetics", following the Y chromosome by using surnames. I thought that China with its ancient records would be a great place to use this technique to study population structure and migration. So I put Du Roufu in touch with Luca Cavalli-Sforza and they have carried out an extensive collaborative study.

Introduction

Genetics a twentieth century science, yet it was built on solid footings from earlier years. The nineteenth century brought us Darwin's theory of evolution; the shocked intellectual world has never been the same. The century brought Galton's introduction of quantitative methods for studying inheritance and his approach to the separation of nature and nurture by using twins. It brought Weismann's distinction between germinal and somatic tissue. And, it brought an understanding of chromosome behavior and meiosis. But, above all, it brought Gregor Mendel and his experiments with garden peas, so simple and so beautiful, and so unappreciated at the time.

Mendel was the hard-luck guy of nineteenth century biology, destined to have his work misunderstood or ignored. This was true, not only in genetics, but in other fields, for example meteorology and bee breeding. In meteorology his pioneering work, such as using the recently developed telegraph to forecast weather for local farmers, as well as more basic work on cyclones, was unrecognized in the larger world until after his death. In bee-breeding he was frustrated by the queen bee's stubborn refusal to mate except in the clouds. Mendel's later years were spent fighting administrative battles, and his research suffered — a phenomenon not entirely unknown in our time. Alas, only after his death was he suddenly transformed from an obscure Abbott to a scientific celebrity.

The science of genetics began with the triple rediscovery of Mendel's rules, by three scientists in three different countries. It was immediately apparent that Mendel's factors followed the rules that cytologists had recently worked out for chromosome behavior. Many

people must have seen the connection, but the ones who wrote about it most convincingly were Boveri in Germany and Sutton in the United States. The chromosomal basis of heredity was immediately accepted by almost all geneticists, although the definitive proof waited until 1916 for Bridges' nondisjunction experiments.

It is convenient to divide twentieth century genetics into two periods, each about 50 years. A more precise dividing time between the old and the new genetics would be 1953, the date of Watson and Crick's great discovery. But I'll speak in round numbers. In the first 50 years genetics was dominated by breeding experiments and the microscope — transmission genetics and cytogenetics.

The second period started out by being dominated by microbes and molecules, tiny organisms and enormous molecules. During the half-century, the techniques — beautiful, powerful techniques — became increasingly chemical and the computer has played an indispensable role.

I would like to refer to the driving techniques of the two periods as the two M's and the two C's. In the first period the two M's were mating and microscopy. In the second period, the two C's were chemicals and computers.

On seeing the program of this Congress, I imagined myself as a Rip Van Winkle who had gone to sleep in 1950 and had just awakened. (For those not acquainted with Western lore, Rip Van Winkle was a character who slept for 20 years and awoke to a greatly changed world.) I took a casual look at the program. Here is a short list of words -- mostly taken from the program titles or suggested by them -- words that did not exist in 1950, or whose meaning has greatly changed. I have put them in alphabetical order.

Anticipation (formerly an ascertainment concept, now cytological); apoptosis (now studied genetically); BAC clones; *Caenorhabditis elegans*, Zebrafish, Puffer fish, *Arabidopsis* (of course these species existed, but no western geneticist had heard of them, although fugu was well known to Japanese); central dogma; clone (all sorts of new meanings); coalescent; concerted evolution; cosmid (could anyone from pre-1950 guess the meaning?); DNA amplification; double strand breaks; down regulation; endoplasmic reticulum; enhancer; epigenetic (old word with a new meaning; maybe the new meaning is a mistake and another word should have been employed); fingerprints (again a new meaning); fluorescent in situ hybridization (better know as FISH); fragile chromosomes; genomics; HLA; Holliday junction; homeobox; hybridization (another old word with a new meaning); junk DNA; knockout; LINEs and SINEs; messenger RNA; molecular clock; mutators (actually mutator genes were known but not understood); nucleosome; origin of replication; PCR; VNTR; physical map; prion; promoter; pseudoautosomal; QTL; rDNA; restriction enzyme; retrovirus; retrotransposon; signal transduction; synaptonemal complex; telomere (Muller had invented the word, but the structure has been quite different from what he envisioned); transcription; translation; transgene; transition; transversion; transposon; Xist.

I could go on, but I want to save time for saying other things. So let me return to the first 50 years

The First 50 Years

Soon after the discovery of the chromosomal basis of heredity, the role of sex determination became an important issue. Did sex follow Mendel's laws? It was immediately apparent that it could be thought of as a repeated Mendelian backcross, but was there a gene? A pair of heteromorphic chromosomes, called X and Y, clearly played a role in sex determination, but the earliest workers had them confused. It was left to a bright young woman, Nettie Stevens, to straighten it out. She showed clearly in an insect that the female has two X chromosomes and the male an X and Y. But the generality was not clear. Doncaster, studying moths, found genetic evidence for sex linkage, and the evidence pointed the other way. It is not hard to image the confusion that ensued. The correspondence between cytological behavior of X and Y chromosomes and the rules of sex-linked inheritance were thrown into doubt. It was straightened out a few years later by the Morgan school, studying sex-linkage in *Drosophila*, and by the realization that in lepidoptera the female sex is heterogametic.

Another early example of different conclusions reached by studying different organisms arose with silkworm genetics, developed to a high point in Japan. As I mentioned, female sex is heterogametic in moths. There was another difference, however. In *Drosophila*, sex is determined by the number of X chromosomes and their relationship to the number of autosomes; the Y is not involved. In the silkworm, the Y is the determining element. American geneticists automatically assumed that humans would behave like big *Drosophilas*. I recall a paper, which explained a curious human inheritance pattern by invoking the *Drosophila* model of attached-X chromosomes. For all I know, Japanese geneticists reached the opposite conclusion and preferred the Y chromosome determination. In any case, as everyone in the room knows, the silkworm model was the one elected by mammals, and the results in mice and men came as a major surprise to most western geneticists.

Many things that were thought to be understood have turned out to be different, or at least more complicated. An example is Haldane's rule, formulated in 1922. It says that, in interspecies crosses whenever one sex is inviable or sterile, it is usually the heterogametic sex. When I was in graduate school, I thought I understood the reasons. Now, as has been brought out abundantly in this Congress, the better methods of analysis now available have shown the story to be considerably more involved.

The first half-century was characterized by a futile search for the gene. Many experiments were an indirect attempt to get at the nature of this elusive object — for example by studying mutation. But most geneticists simply regarded the question as insoluble — something for the future — and studied other problems.

I started graduate school in 1937. I well remember my feeling at the time, and I think it was general, that it would be many years before we would know what the gene really is. Certainly it would not happen in our lifetime. It seemed to be the most elusive of objects, and many thought we would probably have to understand the full details of gene action before we understood the gene itself. Hardly anyone thought of the gene as one-dimensional, although I am informed that Koltsov suggested a double-helical structure.

Transmission genetics was essentially solved early in the century. The main principle, of course, was Mendelism. Linkage was a conspicuous exception, but this was solved by the Morgan school and Sturtevant's construction of a linkage map. By the time of World War I, geneticists knew all they needed to know to develop breeding methods. Transmission genetics was a mature science; ready to be exploited. And it was exploited, in countless agricultural experiments throughout the world.

Chromosome mapping became an important activity. In organisms with short life cycles and large progeny numbers, such as *Drosophila*, progress was rapid. In the Orient the silkworm was the center of mapping activity. Among plants, maize was the most completely mapped. The Sixth International Congress of Genetics, held at Cornell University in 1932, featured a living chromosome map of maize in which plants with mutant genes were planted in rows corresponding to their chromosomal position. I recall a similar living map for the morning glory, which was a feature of the first Japanese postwar genetics symposium in 1956. But progress in human gene mapping was essentially nil.

World War II brought a halt to genetics research in many countries. One of many tragic examples occurred in Japan. *Drosophila ananassae* was a favorite species there. A substantial linkage map was constructed and this species had the interesting property of male crossing over. Alas, despite four replicate cultures kept in widely different places, all the strains were lost during the war. Dr. Moriwaki, who suffered the loss, was also the discoverer in 1936 of cytoplasmic transmission of Leber's optic atrophy, although of course he had no way of knowing that the cytoplasmic elements were mitochondria.

During the first half-century, cytogenetics came into its own. Chromosome breakage and the consequences thereof — inversions, translocations, deletions, and duplications — became a part of the geneticist's tool-kit. The finest development was in maize, culminating in Barbara McClintock's exploitation of the breakage-fusion-bridge cycle, with ramifications that seemed incredible at the time but are now commonplace. Maize, because of its beautiful pachytene chromosomes, was the species of choice in the United States. In the Orient, Trillium was exploited. *Drosophila* got a big boost with the discovery of giant salivary gland chromosomes. Cytogenetics was particularly pleasing to study, for you could draw a picture of what ought to happen and it usually did.

Human cytogenetics was pitiful. The X and Y chromosomes had been identified, but incredible as it now seems, the chromosome number itself was in doubt. I have the dubious distinction of having studied with the man, T. S. Painter, who first reported the wrong number,

48, that dominated textbooks for a third of a century. Painter also made another mistake. C. B. Davenport, praised for his genetic zeal and damned for his eugenic naiveté, had postulated, as had several others, that Down's syndrome is caused by trisomy. He obtained some cellular material and asked Painter to look at the chromosomes. Painter looked and could find no abnormalities. I have often wondered if this error delayed the discovery that trisomy is in fact the cause. Let me quickly add, however, that Painter was really an excellent cytologist; the problem was the inadequate techniques of the time. His luck changed in 1936 when he showed that salivary gland chromosomes really were chromosomes, thus opening up the fertile field of *Drosophila* cytogenetics, so richly exploited by Bridges, Muller, Sturtevant, Dobzhansky, Lewis, and many others. How different it is now. Whereas in the early days you couldn't even count human chromosomes, now all you have to do is recognize different colors. A child, unless color-blind, can do better than the most skilled cytologist of only a few years ago.

I am pleased that T. C. Hsu is attending this Congress. T. C. was a student of C. C. Tan. He is the person who catalyzed the renewed study of human chromosomes by the discovery of the chromosome-spreading effect of hypotonic solution. This led directly to the determination of the correct number. In those early days we didn't know what human chromosomes looked like and one person showed a picture of what were presumably his own chromosomes, but these turned out to be a contaminant from some other species. Contamination was common in the early days of human cell culture.

Another aspect of cytogenetics, polyploidy, was widely exploited in the first half-century. A large number of agricultural and ornamental plants turned out to be polyploid. Allopolyploidy provided an easy way to obtain fertile hybrids between strains in which the diploid hybrids were sterile. Colchicine and other polyploidy-inducing drugs made the task easier. Increasingly this has become a part of the plant geneticist's bag of tricks.

Mutation was first described by deVries in the early days of the century. His mutations turned out not to be gene mutations, but rather to be segregants from complex cytogenetic heterozygotes; but he had the right idea. For a quarter century, mutation was something outside of experimental control, almost like radioactivity. Then in 1927, H. J. Muller and simultaneously L. J. Stadler reported that ionizing radiation greatly enhanced the mutation rate. Muller's great contribution was not so much the idea of radiation mutagenesis, but rather his developing a technique, the *CIB* method, which permitted unambiguous quantitative determination of mutation rates. With this discovery, mutation became an experimental subject. Most of the studies were kinetic — effects of dose, dose-rate, and fractionation. And such studies did not yield the hoped-for insight into the nature of the gene.

More surprising was the long interval before the discovery of chemical mutagens. Looking back over the old literature, one sees several examples of what were probably successful experiments, but the mind-set of the time was against it. The standard of proof was set so high that few experiments met it. One of the early discoveries was Rapoport's finding that formaldehyde is mutagenic. I am happy to note that Svetlana Vasilieva, who is attending

this Congress, was once an assistant to Rapoport. The discovery of the mutagenesis of mustard gas is a remarkable story. J. M. Robson in Edinburgh had noticed that mustard burns resemble those caused by radiation. This suggested that mustard might be mutagenic, and this possibility was discussed by H. J. Muller and Charlotte Auerbach while Muller was in Edinburgh. Auerbach's experiments were dramatically successful, and by this time Muller had moved to the United States. He had learned of her results, but since they involved a war chemical, they were regarded as a military secret. I remember visiting Muller during this period. He asked me if I had learned of Auerbach's work, obviously hoping to discuss it. I had not heard of it and waited for him to tell me. He said no more and changed the subject, leaving me puzzled. I realized that something was afoot, and discovered what it was only after the end of the war when the results could be publicly discussed.

After the war, came what Muller, in his Pilgrim Trust lecture delivered in 1945, called "the coming chemical attack on the gene". And what a magnificent prophesy it was

Shortly before the end of the half-century a new element was introduced, the study of microorganisms. Joshua Lederberg's demonstration of recombination in *E. coli* started a rush for the gold found in microorganisms. At the same time the phage group, with Delbrück as its intellectual leader, became equally prominent. Benzer had mapped phage genes and driven the subject into the ground, to a resolution comparable to the size of large molecules. Fine-scale genetics and the chemistry of large molecules had met.

During the first 50 years the greatest beneficiary of genetics was agriculture. Plant and animal breeders had long produced spectacular results by selection. One doesn't have to understand Mendelism to realize that "like begets like". Cattle breeders selected for milk or beef production, horse breeders produced draft horses, riding horses, and ponies; and dog fanciers got carried away, producing all manner of bizarre objects. But with Mendelism came the basis for dealing with single-gene traits, usually complicated by dominance, which blending inheritance couldn't handle. Also, quantitative genetics theory, based on Mendelism and developed by Fisher and Wright made selection more quantitative, and more effective.

The most striking success story in the new world was hybrid maize. With Mendelism came the understanding of inbreeding depression. There was debate, and still is, about the possible role of overdominance, but the absence of this knowledge did not deter the rapid practical progress. Breeders developed inbred lines, selecting them for ability to combine with other inbreds to produce good hybrids. Since hybrid maize was introduced in the 1930s the yield per hectare has increased by about 5-fold. Of course, part of this is due to better management and agronomic practices, but more than half, estimated at about two thirds, is due to genetic improvement.

I want to add that R. A. Fisher, in addition to setting forth the basis of quantitative genetics in 1918, also introduced efficient statistical design for field experiments. I have no idea how much the improvement of agricultural performance owes to this one man, but it surely is a great deal.

Another major advance in the first 50 years was bringing genetics into our understanding of evolution. Darwin came close to saying it all, but the big gap was the nature of inheritance. Mendel of course filled it.

The combination of Darwin and Mendel led by the 1930s to the new synthesis. The theoretical basis was laid mainly by Haldane, Fisher, and Wright. Fisher had already supplied the answer to what had bothered Darwin and his critics, and perhaps led to the Lamarckian views in the later editions of his book. In this sense the successive editions of "The Origin" got worse and worse. At the center was the question of decaying variability. Under the prevailing view of blending inheritance, variability is lost very rapidly, as with intense inbreeding in Mendelian populations. With Mendelian inheritance, variability is conserved and a very small input of mutation is sufficient. Although the amount of variability in natural populations is an object of continuing study, it no longer seems mysterious.

The three pioneers provided a mechanistic theory of evolution, based on the solid foundation of Mendelian inheritance, that permitted deductive conclusions and offered the opportunity for tests. But there were rather few opportunities for real quantitative testing. Haldane used data on the evolution of industrial melanism in moths to estimate the selection intensity, but such good examples were few. The beautiful quantitative theory, developed by the three pioneers and extended by Kimura, found its deepest use in the second 50 years after the advances created the new science of molecular evolution.

What Might have been Discovered, but Wasn't

Before moving to the second half-century, it might be of interest to note some things that were not discovered until later that could very well have been found earlier. By this, I mean that they did not require any techniques not available at an earlier time.

The admonition of Bateson and Bridges to "treasure your exceptions" was often stated, but I now think, not followed often enough. Bridges, however, followed his own advice. His use of non-disjunction to prove the chromosomal basis of inheritance is a classic, although by 1916 it was no longer needed. But it was a magnificent paper and was the very first article to appear in the new journal, *Genetics*.

Here are some things that were discovered later and might well have been found earlier. Were they simply overlooked or ignored as uninteresting?

- Imprinting. One gene after another in humans has been found to show imprinting. It is not surprising that this was not noticed in small human pedigrees. But it *is* surprising that it was not noticed in the mouse and other rodents, where careful breeding studies were done? Differences in reciprocal crosses should have been easily noticed. Furthermore, there was solid work on such phenomena in mealy bugs and *Sciara*. These were regarded as curiosities rather than as possible leads to a deeper insight. Were geneticists simply too

wedded to Mendel's rules, so that they regarded exceptions as uninteresting exceptions or experimental errors?

- Transposable elements. Early in the century, Emerson had observed variegated maize kernels. Demerec had puzzling examples of instability in *Drosophila virilis*. But none of these studies attracted much attention. Demerec went on to other things and his earlier work was almost totally ignored.
- Meiotic drive: The abnormal segregation of the t-locus in mice was well worked out. But the general view was that this was a rather uninteresting exception. Rhoades' beautiful analysis of meiotic drive in maize, produced by the formation of neo-centromeres was largely ignored. Meiotic drive became a popular subject only later after it was found in a number of other organisms, especially *Drosophila*.
- Anticipation. This was explained as a statistical artifact, due to ascertainment bias. This still may a part of the explanation. But now we know that the phenomenon is real in Huntington's and several other diseases, caused by instability of trinucleotide repeats. Although the cytological mechanism could not have been discovered then, the reality of the phenomenon surely could have been. It was too easily explained away as an ascertainment artifact.
- Gene conversion. Carl Lindegren's work in yeast was laughed out of court and other explanations were sought. For example, one could explain many of his results by assuming polyploidy. So conversion was rejected by most geneticists of the time.
- Subdivision of the gene: C. P. Oliver found evidence for crossing over within the gene in *Drosophila*. But ruling out mutation was very difficult until ways of recovering reciprocal products were developed. The notion that the gene was indivisible was widely prevalent and evidence for subdivision was resisted.
- Chemical mutagens. I have already mentioned the reluctance to accept data that hindsight shows us were providing pretty good evidence
- Kin selection and parental expenditure: These were clearly understood by Fisher, and Haldane alluded to kin selection, but neither chose to exploit it. These ideas, central to modern theories of behavioral evolution, were clearly explained in Fisher's book in 1930. Yet it took many years for Hamilton to awaken interest in the subject.
- Antibiotic and pesticide resistance. Penicillin and DDT both were discovered and exploited during World War II. Students of evolution could easily predict what would happen, and some writers did, but there was no serious general discussion until later. And there was no attempt at concerted action, nor is there much today.

- Recombination in bacteria. Early experiments to search for recombination in bacteria failed because they were not designed to detect rare events. The ideas Lederberg employed so successfully in 1946 could have been used earlier. But bacteria were widely regarded as sexless.

Why this blindness to phenomena that are such a large part of our current thinking? I believe there are two major explanations.

First, there was a widespread search for and belief in generality. Some of the things that led to this belief were the regular occurrence of Mendelian inheritance, the general similarity of meiosis in the various species studied, the construction of gene maps on simple principles, and the way in which the consequences of cytogenetic changes could be predicted. As a result, geneticists were encouraged to believe in the complete generality of what had been discovered in a few favored species. Generality was the *Zeitgeist*. Deviations from conventional expectations were often attributed to viability differences or technical errors.

A second factor was noted by George Beadle. He mentioned what he regarded as a curious preference for randomness. The symmetry and the random aspects of Mendelian segregation and recombination were very seductive. An example is the acceptance of no chromatid interference in meiosis. The evidence for this, mainly from studies of attached-X chromosomes in *Drosophila*, was not very strong. Yet the conclusion was universally accepted.

Was this preference for generality, symmetry, and randomness good for the field or bad? Probably both. Clearly it aided in working out general principles. Population genetics advanced rapidly by making this assumption. Yet, I also suspect that a number of phenomena not discovered until after 1950 might well have been found earlier, if geneticists had been more willing to trust their data and treasure their exceptions.

In 1950 the gene was still elusive. Long before, Muller had told us what the gene has to do. It has to carry information; it has to replicate itself with superb accuracy; but when there are errors, it has to copy them with the same accuracy, that is mutate; and it has to exercise control over development and physiology.

The Transition: A Remarkable Decade, 1945-1955

Biochemical genetics and the relationship between genes and enzymes was not new. It had been started by Sir Archibald Garrod in his discovery of inborn errors of metabolism near the turn of the century. But the work of Beadle and Tatum in *Neurospora* sent the subject off on a new course. Sewall Wright once told me that he had thought of writing a book on developmental genetics, based heavily on his guinea pig studies, but the *Neurospora* work clearly told him that there was a new direction. The field of biochemical genetics was forever changed, and he didn't write the book.

In 1946 Joshua Lederberg, working with E. L. Tatum, discovered recombination in bacteria. The great resolving power that comes from having enormous numbers and the capacity to select very rare events were immediately appealing. It was only a few years until *E. coli* became the best understood of all organisms, completely eclipsing maize and *Drosophila*. At the same time phage genetics also had an explosive growth.

While this was going on there was increasing evidence for DNA as the genetic material. The evidence had already been strong from the Pneumococcus transformation studies in 1944, but for some reason the experiments of Hershey and Chase in 1952 had a greater influence. At the same time the chemistry of DNA was becoming much more solid. In particular, the repeating tetranucleotide structure was found to be wrong, thus making DNA attractive as an information-bearing molecule.

The stage was set, and in 1953 two clever model builders, Watson and Crick, hit on the right structure. The very structure of DNA immediately shouted the answers to Muller's questions. The era of molecular genetics was born, courtesy of Watson and Crick. The gene was no longer mysterious. It was something to be exploited. The central question of genetics had been solved.

The Second Fifty Years

In rapid succession the role of RNA was clarified, the translation of linear DNA information to linear amino acid sequences was worked out, and the genetic code was solved. This is much too familiar to all of you for me to elaborate.

As attention shifted from information transfer to regulation of gene action, the intellectually satisfying operon model of Jacob and Monod took center stage. It was so neat that the genetics world elected it by acclamation. Geneticists began to think of applying the results, and especially the techniques, of microbial genetics to the study of multicellular organisms. A familiar quip of the time was that all we know about differentiation is from organisms that do not differentiate.

At that time everything seemed beautifully simple — replication, a universal code, transcription, translation, a central Dogma. And then the complications set in. So genetics was no longer a subject in which a few simple principles could explain everything. The devil is in the details, and you had to know them.

Whereas the first 50 years was devoted to a failed effort to learn the nature of the genotype by studying phenotypes, the second 50 years have been dominated by the using the genotype to understand the phenotype. The study of genetic control of development is now in full swing.

In the first 50 years genetics was limited by the paucity of available techniques. It is astonishing, nevertheless, to note how much was learned about *Drosophila* by the use of the many special strains that were developed, particularly by Muller and Bridges. It is equally astonishing how much Barbara McClintock could see by examination of chromosome breakage and color patterns in the maize endosperm. But the techniques were few. With such a limited bag of tricks, successful genetic experimentation depended on cleverness — and also on a great deal of time and patience. The past 50 years have been characterized by a truly astonishing cascade of new techniques.

The techniques are so good -- so efficient, so easy, and so accurate — that a beginning student can sequence a gene, something that was a daunting task to the best team of experts not long ago. I'll not dwell on these techniques; they have been abundantly evident throughout this Congress. The subject is technique-driven, but who can complain when the techniques are so powerful?

We are just beginning to use molecular methods for genetic dissection of common multifactorial traits. It is too early to guess just how soon this will be practically useful, but the ultimate importance can hardly be in doubt. Yield factors in cereals and vegetable crops have been identified. Soon they will be exploited. There is good progress in understanding human multifactorial diseases.

Molecular biology has brought a totally new subject, molecular evolution. The genetic study of species differences used to be confined to those species that could be crossed. The arguments of skeptics of the time who thought that chromosomal differences applied only within a species or between very similar ones were difficult to counter. Geneticists had to rely on a faith that the same principles that govern small difference also apply to large ones, but the definitive, convincing proof was lacking.

Now, no such limitation applies. DNA comparison between widely different organisms is now so commonplace that it is hard to realize that in the not distant past this was impossible. Geneticists expected that homologous genes would be found between distantly related species, and that the genes would have diverged in function. They expected that gene duplication would lead to new functions, and that some duplications would mutate themselves out of functional existence. But suspecting this and proving it are different things, and we had to wait for appropriate molecular techniques.

Motoo Kimura dropped a bomb when he suggested that the great bulk of molecular change is neutral, driven by mutation and buffeted about by random drift. The jury is still out on the question of what fraction of genetic change follows this paradigm, but there is no doubt that much does, especially in non-coding regions. From this has grown a workable molecular clock and the possibility of far better phylogenetic analysis.

We have an abundance of genes that have hardly changed over very long periods, maintained by purifying selection. We have genes that have changed much too rapidly to be mutation-driven, and hence are the result of positive or stabilizing selection. And we have

junk, presumably mainly neutral. Traditionally, the study of evolution has dealt with form and function, and that is still where much of the interest lies. But with a solid underpinning of molecular change, the subject proceeds in a much more rigorous way. And molecular studies, mitochondrial DNA in particular, are now clearing up a topic in which we are all interested, human ancestry.

Now researchers are chipping away, carving a sculpture out of a very hard marble block. The two big problems — the nature of development and the nature of the mind — are being subdued. I don't know whether there will be beautiful, general theories to come out of this — something really nice like Watson and Crick found — or whether it will be an accumulation of more and more details. I'll confess to a secret hope for the former.

The accomplishments of modern genetics are indeed astonishing, especially to one like me who grew up in the classical period and is having a hard time growing out of it. Consider the following:

Temin and Baltimore have revealed a new kind of virus, the retrovirus. It came as a surprise, but is now a well understood extension of the Central Dogma. Retroposons are turning up everywhere, and not only are they turning up now, they have long been a factor in a long evolutionary history and have left their footprints. And, I needn't remind you that the HIV virus is a terrible scourge and a major challenge to our ingenuity..

We have also seen an important role for RNA, not only as a vehicle by which DNA imposes its information on development. There is now good reason to think that there may have been an RNA world, before this was replaced by our present, presumably more efficient DNA-centered organisms.

QTLs (quantitative trait loci) rely on an old idea —the use of linked markers to locate genes of interest. The difference is again a matter of technique. QTLs can now be discovered efficiently and these procedures have yielded results in several plants — tomatoes, maize, and rice, to name three. This will also be useful in livestock breeding. And they will help unravel the mode of inheritance of complex human conditions. Only a few months ago came a report of a QTL associated with high intelligence, the first opening in the door to a detailed genetic understanding of important human behavioral attributes.

One organism after another is having its DNA sequenced. Just last month the sequence of *Treponema pallidum* was reported. This is significant, not because of its size, for this is a relatively small organism, but because it causes a major disease. And, more important, it has resisted study by the ordinary methods of bacteriology. Sequencing will surely open up new avenues. Very early in the next century the complete human sequence will be known. What seemed like an unattainable end point of genetics in 1950, complete knowledge of the individual genes and of the genome will soon be achieved. A major task in the century ahead is to take this great store of information and make sense of it.

If I were talking in North America I would emphasize maize and wheat. But we are meeting in Asia, where rice is the major food crop. Rice is a particularly inviting target for sequencing. In the first place, it is an important crop, grown throughout the world. It feeds countless people, and it is usually eaten by people rather than fed to livestock. The world badly needs improved rice. Its great advantage for sequencing is its small genome size. It is the smallest of the cultivated grasses. Its 12 chromosomes include 430 megabases of DNA, only one sixth the number in maize, and far fewer than polyploid wheat. The green revolution brought a large increase in rice yields, but recent progress has been slower. There is room for great improvement by both standard breeding methods and by newer techniques. For example, finding QTLs in wild relatives may provide a source of new, valuable genes. It can certainly help in identifying potentially useful qualitative traits. Can we develop varieties that perform well with less fertilizer and pesticides, and especially with less water, surely the most important limiting factor? Japan, Korea, and China are deeply involved in the rice genome project. Will the complete sequence provide a quantum jump in practical knowledge? I hope so. Perhaps rice will provide the first chance to see just how practically useful the complete sequence is.

So far gene therapy has not had much success. Its best chance is with certain kinds of rare diseases. Then there is the practical problem that manufacturing chemists are not likely to spend the necessary money for a rare disease. Nevertheless, there are bound to be modest successes. And if we can repair the genes causing, for example, Tay-Sachs disease or cystic fibrosis, people will begin to think of getting rid of them? I suspect that parents would welcome this. I for one would be happy to live in a world in which these genes and many other misery-causing ones had become extinct. Of course, we are not likely to prevent mutation any time soon.

The papers have been full of Dolly, the sheep that is said to be a clone derived from an adult, differentiated cell. The evidence that this is a real result and not an error has been strengthened by recent DNA analysis. But more impressive is the result of Dr. Wakayama, who has produced several cloned mice including clones of clones. They promise an answer to a host of interesting questions. Why does the success rate remain low? Is it technical imperfections, or fundamental? How will imprinting affect the process? Is imprinting preserved or erased in differentiated cells? Will these cells show the cumulative wear and tear of aging? What happens to the inactive X in females? How soon will cloning high-performing dairy cows be practical? Will society deal rationally with the ethical and religious issues raised by possible human applications?

Genetics has pervaded almost every branch of biology. Does this mean that it will lose its identity, as it spreads its tentacles in many directions? Will we no longer have genetics departments? The next century will tell us.

Genetics and Society

The great advances in molecular genetics will surely have correspondingly great consequences. Early in the next century the sequencing of the many genomes will be complete. We can easily see the potential benefits -- more food, better diagnosis and treatment of disease, better ways to identify people killed in accidents, better understanding of complex traits such as intelligence and emotions. We can also anticipate problems. They are being discussed *ad infinitum*. Will the intrusion into privacy be a major threat to our liberties? Will the possibilities be exploited to our detriment by industry or government? The opportunity for good and bad are both great. Much can be foreseen and planned for, but much cannot. Will societies accept this knowledge and use it wisely? As Hamlet said "That is the question".

In the twentieth century genetics has been the victim of two ruthless dictatorships. Hitler carried racist eugenics to ridiculous and tragic extremes. Stalin enshrined Lysenkoist genetics, again perverting our science and again producing tragic consequences. We can easily imagine such extreme views in the future. But what those two regimes had in common was that both were ruthless dictatorships. That is the problem. I recall hearing H. F. Kushner, speaking in Japan in 1956, reporting inherited effects of blood transfusions. I am certain that he knew better, for he was well known traditional geneticist in an earlier period. We can't expect scientists to behave honestly and rationally when a gun is pointed at their heads.

Chinese genetics has been through difficult times, but it is now on the upswing and progress is very rapid. That is apparent throughout this Congress. At this Congress we had a free and open discussion of the Maternal and Infant Care laws. I am aware of my limitations in understanding another culture, with its long and magnificent traditions. I am also aware that my own society is not above reproach, for example in its continued confusion over therapeutic abortion. But I will venture three comments:

(1) The word "eugenics" now has so many different meanings, many of them highly pejorative, that it has lost its usefulness. As Ren-Zong Qiu has pointed out, the Chinese word *yousheng* can as well be translated "healthy child". It would be good for something like child health to be used rather than eugenics.

(2) The wording of the law and especially the English translation is open to various interpretations. I hope it can be interpreted that there is informed consent and that acceptance of counseling advice is not mandatory. At the same time the counseling should be as accurate as possible in predicting the risk of children with various impairments.

(3) Finally the value of scientific contact and policy discussions among geneticists in all countries can only be good, and I would encourage more. We have much to learn from each other. This Congress is an important step. Let me add my belief that we should welcome comments from Chinese geneticists on genetic practices in our society.

Of far greater urgency and much closer at hand than any consequences of changing gene frequencies is the total world population. Unless the world-wide birth rate is brought into

some sort of balance with food supply and economic realities, we may not have the luxury of worrying about our genetic constitution.

China has 22 percent of the world population but only 7 percent of the arable land, and this land area is being reduced by erosion and diversion to other uses. There is certain to be conflict between individual freedom to reproduce and the social necessity that reproduction be limited. China is the first large nation to face this problem and act decisively. The rest of the world awaits the effects.

Envoi

I have lived through 82 percent of the twentieth century. I have seen the tremendous growth of our fundamental knowledge. I have seen what once appeared to be beautifully simple -- Mendelism, linkage maps, the Watson Crick model, the genetic code -- grow in depth and complexity. We are developing the techniques to manage this complexity. But do we have the individual and social will? The twenty first century will tell.

You young people in the audience have an exciting time ahead. I would like to start over and join you, but I'm afraid that is not a viable option. I can hope, however, to see you again, early in the next millennium at the next congress in Melbourne.

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