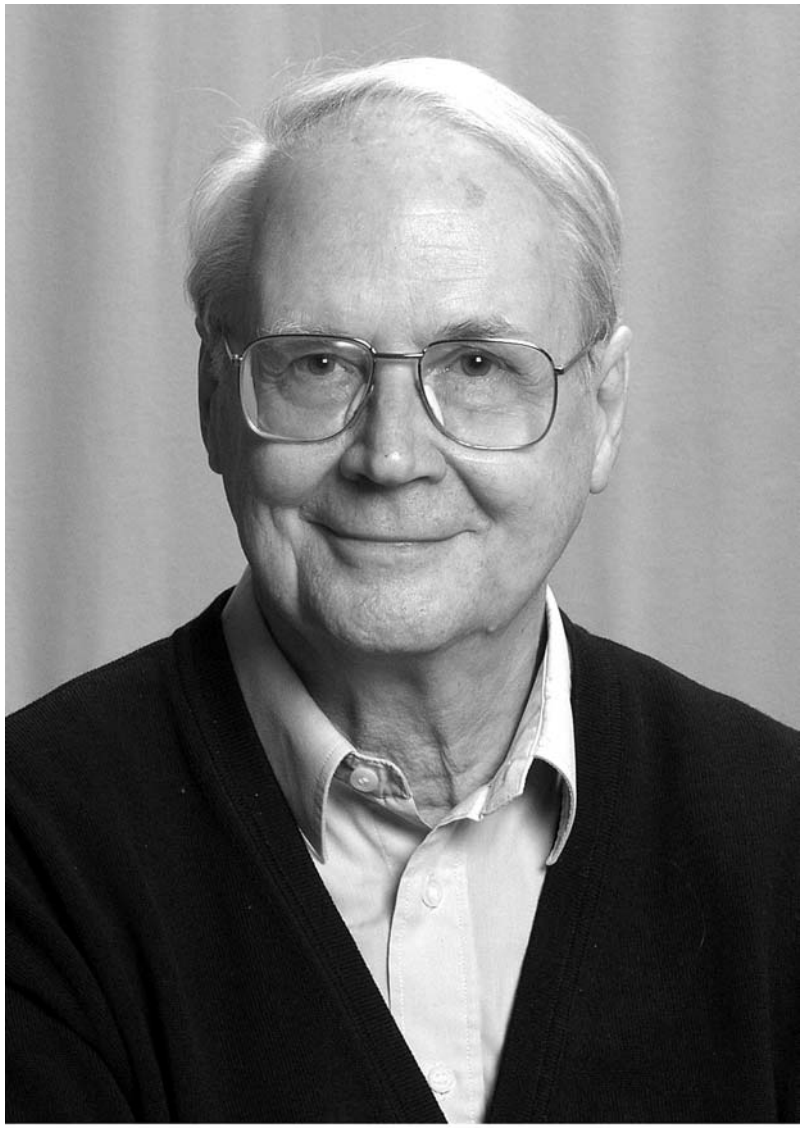

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Fifty Good Years

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Contents

EARLY YEARS IN POSTWAR GERMANY

Compared to our parents' generation, my generation has been a lucky one. Our parents lived through really hard times: two World Wars, the big inflation of 1922/23 that wiped out any savings—if there were any, the Great Depression, the Nazi rule with its crimes (and with its temptations), and for many, long years spent as prisoners of war[1].

True, we also lived during the war, but we were children, and afterwards things gradually became better, and soon much better. After the turmoil of the last months of the war, I found myself in northern Germany. I finished high school, enrolled in the university as a medical student, and, by a stroke of luck, entered the department of biochemistry, where I spent most of my time during the next two years under the guidance of the late Hans Netter, a very amiable and knowledgeable man with a strong bent toward physical chemistry. He was an enthusiastic teacher, very interested in the application of physical chemistry in biology, about which he wrote books well known in Germany. The little I have learned of thermodynamics and kinetics I owe to him. However, after two years, I felt that I should move on to something different. I started looking around for other institutes in Germany to finish my medical studies and to earn an M.D. and decided that Butenandt's institute in Tübingen was my first choice.

Adolf Butenandt was head not only of the Max Planck Institute for Biochemistry, which had many research groups but was also professor of physiological chemistry in the medical faculty. This was a different world. Nucleic acids, which in Kiel had been but a footnote, were here already the topic of the day. Butenandt, best known for his work on steroid hormones, which earned him a Nobel Prize[2], and later as president of the Max Planck Society, had also initiated research on other topics. Collaborating with Alfred Kühn, the director at a neighboring Max Planck Institute, Butenandt became interested in gene action and found that kynurenin was an intermediate in the formation of the red eye color of *Drosophila* at about the same time that Ephrussi and Beadle were engaged in such work in France (1). Butenandt also initiated a virus group after he heard Stanley talking on the crystallization of tobacco mosaic virus, a finding that at that time excited many discussions on the nature of life.

When I entered the department in 1952 and became a student in this virus group, nucleic acid was a household word. Interesting and vivid lectures were given on this topic, e.g., by Hans Friedrich-Freksa (who became my thesis supervisor), by Gerhard Schramm (who together with Alfred Gierer and Heinz Schuster later showed that the RNA of tobacco mosaic virus was infectious by itself and that deaminating its cytosine caused mutations), and by Wolfhard Weidel (who had been a coauthor of the 1940 paper on biochemical genetics in *Drosophila* with Butenandt and Becker). Avery's experiment was well known, as was Chargaff's discovery that the base composition of DNA is different in different organisms, but identical in different tissues of the same organism, which was considered in keeping with a genetic role for DNA. The A = T and G = C rule was also known, but was not interpreted any more in Tübingen than by the author himself. That

[1] These were the lives of the average German family like the one from which I came. The fate of those who were persecuted by the Nazi regime for race or political reasons and of whom a vast majority perished in the Holocaust was incomparably harder.

[2] He was not allowed to accept this prize because Hitler had decreed that no German could accept a Nobel Prize after a well-known journalist, Carl von Ossietzky, tortured to death in a concentration camp, had been awarded the Nobel Peace Prize. Butenandt obeyed and stayed in Germany as head of the then Kaiser Wilhelm Institute for Biochemistry. Recently, it has been asked whether a scientist in such a high position could have avoided knowledge of the unethical and even criminal research going on in Nazi Germany and even in other institutes of the Kaiser Wilhelm Society. Such investigations may be necessary to understand those dark times. However, not having been around at that time, I do not know how to judge. I do not know what I would have done, in those days, hearing about such research. What I do know is that it is a great privilege to grow up in a society that offers many—and conflicting—views and actions to choose from. This was another privilege of my generation in Germany.

had to await Watson and Crick, a year later, but before that, Hershey and Chase's experiment on DNA being the genetic constituent of bacteriophage was much hailed. The double helix was even more admired, not as a strange surprise, but rather as a wonderful confirmation of the DNA's role in self-replication.

The first reading I was assigned was not an old textbook, but the 1951 volume of the Cold Spring Harbor symposia, in which I discovered a very interesting but, at that time, certainly not well understood (by me) article by Barbara McClintock (9).

THE COLOGNE INSTITUTE FOR GENETICS

I spent four years in Tübingen, after which I moved to a medical research laboratory in an effort to begin a medical career (which turned out not to suit me). By a new stroke of luck I met Max Delbrück, who invited me to give a seminar in Cologne. Here, a small chair of microbiology was just being established at the botany department, and its new head, Carsten Bresch, offered me a position. This offer could not be declined. Soon I learned that much more was to happen. Josef Straub, at that time director of the Botany Institute, had the ambition to improve the Cologne biology. He had tried to persuade Delbrück to take the chair of this new microbiology group, but that was no real offer for a full professor at Caltech. However, Delbrück agreed to teach one of his famous phage courses in Cologne[3], where he and Straub learned to like each other. Delbrück not only had suggested Bresch for the chair, but, together with Straub, conceived the plan for a big institute of genetics that not only should bring the still new science of molecular biology to Cologne, but which also should be organized more like a department at an American research university than as a traditional German institute.

The times were favorable for such an endeavor. Germany had recovered from the destruction of the war and was now able to invest in less immediate goals. Still, it needed the insight of people to initiate new developments at the university. The combination of the scientific reputation of Delbrück and the skill and amiability of Straub as a negotiator carried the day with the ministry in Düsseldorf (responsible for the University of Cologne). A main point of the deal was that Delbrück was to be the director of the newly founded institute. The small print said that Delbrück's directorship would last only for two years, the maximum time for an extended sabbatical from Caltech, but all people concerned chose to overlook this.

Five small research groups were established and, besides Delbrück and Bresch, the radiobiologist Walter Harm (working on DNA repair) and the biochemist Hans Zachau (soon to be famous for the sequencing of tRNAs) were hired, and I also was given the task of establishing such a group. Later Ulf Henning (who had done distinguished work in Yanofsky's lab at Stanford) joined the institute.

These were exciting years, and they passed only too quickly. After two years, in 1963, Delbrück left, as announced, but unfortunately all the other group leaders also got very tempting offers either in Germany or in the United States, and they decided to leave also. For this reason, the people in my small research group found ourselves in the hapless position of being somewhat stranded, waiting for the departure of our colleagues. Most probably, I thought I would also have to leave because I did not have tenure, and in Germany you cannot get tenure unless you receive a comparable offer from another university. This might have led to the closure of the institute that had inspired so many hopes. I was lucky, however. I got an offer from the Max Planck Society and, consequently, was offered a position at Cologne.

This alone hardly mitigated the aforementioned scenario, but the faculty eventually

[3] Delbrück was German and came from a well-known family of scholars in Germany. His brother Justus was involved in the resistance against Hitler, was imprisoned, and died shortly after the war. Max Delbrück, not liking and not being liked by the Nazi regime and not seeing much of a career there, emigrated to America in 1937 and became an U.S. citizen. He kept contacts in Germany, however, and after the war visited the country several times to encourage young scientists.

succeeded, over the course of the following years, in attracting very capable new professors to the department. Among these were the virologist Walter Doerfler, one of the early investigators of DNA methylation, Benno Müller-Hill[4], who had just, together with Walter Gilbert, isolated the lac repressor, and Klaus Rajewsky, who, within a few years, established the immunology group so well known.

WORK ON TRANSPOSABLE ELEMENTS

In all these years I had not begun to earn the credentials to write a prefatory chapter for the *Annual Review of Plant Biology*. Apart from my thesis work with tobacco mosaic virus, I had always worked with bacteria and bacteriophages, the genetics of which were so interesting in those days, and which were so suitable as laboratory organisms.

In 1959, I met Werner Arber and Jean Weigle during a postdoc year at Caltech. Arber and Weigle had managed to move the *galactose* (*gal*)-operon of *Eschericia coli* to a bacteriophage and I thought that infecting a galactose-negative strain with such a phage might allow the study of gene activity in novel ways. Then I, later joined by a small group in Cologne, worked with the *gal*-operon.

In 1963, Heinz Saedler joined the laboratory and began to experiment with mutants that abolish the activity of the whole operon rather than of single ones of its genes, analogous to the o^o-mutations described by Jacob and Monod in the *lac*-operon. They mapped to the proximal end of the operon but also abolished the activity of the distal genes, which was called a polar effect. These mutants proved unusual. They reverted readily to the wild type and, hence, they were not deletions. However, they did not react to mutagens and therefore could not be the usual base substitutions. What else could they be? Higher organisms show chromosome rearrangements, but these were not well known in bacteria at the time. Was it conceivable that the mutants were chromosome aberrations, like insertions, inversions, or duplications (12)?

This could not be investigated very directly in those days, but Heinz Saedler, soon joined by Elke Jordan, who came as a postdoc from Herman Kalckar's lab, found a way to distinguish inversions from insertions or duplications. Inversions would not alter the length of the phage DNA carrying the *gal* operon, whereas the latter two would. By measuring this length with an indirect method, inversions could be excluded: There was extra DNA (7)!

The same result was obtained at the same time by an American scientist, James A. Shapiro (14). Such coincidences are none too rare in science, showing that the time is ripe for a certain finding. Independent confirmation enhances the confidence in a new result.

Would it also be possible to distinguish duplications from insertions? Georg Michaelis, another graduate student, did this by exhaustingly hybridizing RNA transcribed randomly from the mutant-carrying phage to the wild-type DNA and showing that some RNA remained that only bound to the DNA carrying the mutation in the *gal* operon. Hence, the extra DNA was not a duplication of preexisting sequence in the wild-type DNA. There were even indications that not all of these insertions were different DNAs. If that were true, there might be a bias for certain sequences to be translocated to the *gal*-operon (10).

This was eventually shown by a third graduate student, Heinz-Josef Hirsch, who applied heteroduplex mapping to this question after learning the technique during a visit to Waclav Szybalski, the expert of this technique. In our sample of mutants as well in a sample of bacteriophage λ mutants provided by Ph. Brachet, there were only two distinct sequences that hybridized among themselves but not between the groups. We suggested the designation IS elements (insertion sequence elements) for these entities (6).

[4]He also became well known for his historical work on the euthanasia crimes in Nazi Germany, on which a book appeared in an English translation (11).

It was only then that we realized the relation of these elements to McClintock's transposable elements, in spite of the fact that I had known McClintock's work since my student days, and in spite of a series of seminars that we had held on this topic in the institute in Cologne. Sometimes we are blind (17)!

Nonetheless, our research on the IS elements went on both in our lab in Cologne and in that of Heinz Saedler's, who did some breakthrough experiments in Norman Davidson's lab at Caltech showing that IS elements are normal constituents of bacterial chromosomes and building blocks of plasmids. Upon his return to Germany he became a professor at the University of Freiburg.

While this was keeping us busy and happy, the temptation grew to also get a hand at McClintock's elements. Sure, there were many problems in the mid 1970s, but the new gene technology with its cloning methods had had its first successes, and we reasoned that starting now our work would be slow enough for improvements in these techniques to come along. This proved true, and it was also true that in these years I had the chance to meet Barbara McClintock[5], who helped us with advice and with mutants, as did Peter Peterson from Iowa, who was (and is) also an expert on maize transposable elements.

The speculation that the techniques of gene technology would improve rapidly was correct. Although they did not lend themselves directly to the isolation of a transposable element with completely unknown properties, the techniques to isolate genes with known protein products improved. We chose to isolate the Sh-gene of maize, which encodes sucrose synthase, by looking for cDNA clones binding an mRNA from endosperm that could then be translated in vitro into a protein reacting with an antiserum to sucrose synthase (5). We then looked for novel DNA within the isolated gene in a mutant caused by the insertion of transposable element Ds. This worked eventually (2) and opened the way to study both the gene (18) and the transposable element (3).

What was much more difficult to master for an M.D. and bacterial geneticist like myself was the work with live plants growing in the field or in the greenhouse. Again I was lucky. I met Francesco Salamini in Bergamo, Italy, who not only let us grow our maize plants there (important if your labs are in Cologne, where the climate does not guarantee that maize will grow to maturity), but who taught me and my students (particularly Hans-Peter Döring) to do our crosses right.

Not only were we helped by Salamini in Bergamo, but big changes were ahead in Cologne. The two directors of the big Max Planck Institute for Breeding Research were retiring. Should somebody succeed them or should the institute close? This question is always formally discussed when the director of a Max Planck Institute retires. If the institute were to continue, who should the new director(s) be?

I served a term on the senate of the Max Planck Society at that time and was assigned to the Green Committee, which had to make recommendations on the above questions. I vividly remember the discussions that covered many topics and persons, until, largely influenced by Georg Melchers, then the doyen of the Max Planck botany research, a daring decision was finally made. The first of the new directors would be Jeff Schell, soon followed by Heinz Saedler, by Klaus Hahlbrock, and also by Francesco Salamini. For me, the years to come saw a close association with the Max Planck Institute, an association that proved highly rewarding, both personally and scientifically.

As mentioned, we eventually succeeded in isolating maize transposable elements, as did Heinz Saedler (15, 16) and Nina Fedoroff (4)

[5] Barbara was an antithesis to the modern research professor who runs a big lab. She did everything by herself, not only because she lacked the means to employ many people, but also as a matter of personal choice. She was admirable. After she had been awarded the long-deserved Nobel Prize in 1983, it was often written that she might serve as a role model for scientists. In a certain sense this is true. Still, I think that biology is best served by a multitude of different characters, and that working with graduate students and thus running a bigger lab also has its merits.

in the United States, and working with these elements kept my lab and those of several associates, particularly Reinhard Kunze [who later started an independent group (8)], busy until my retirement[6].

TEACHING GENETICS AND ADDRESSING THE PUBLIC

A university professor not only has to do research but, of course, also has to teach. We gave lectures to our students and also organized courses for people coming from other places, pursuing the tradition of Delbrück's phage course in Cold Spring Harbor. Here we met many outstanding people, later to become leaders in the field of molecular biology in Germany, and thus these courses were, at least for us, very rewarding. We also organized a yearly "Spring Meeting" on the recent progress in the field, which became quite popular, especially among students and postdocs, because we did not charge fees. However, it is often said that we also have an obligation to serve the public and that we have to convey this attitude to our students. How could we do this?

One possibility was to talk about the consequences of our own field on the society. I tried to do this by preparing lectures on plant breeding and on the influence of this on the nutrition of the growing world population. I also happened to be a professor not only of genetics but also of radiobiology, and in this area I gave many lectures on the field in the narrow sense as well as, together with my colleague Hubert Kneser, on the problems, both positive and negative, of using atomic energy.

These activities were not restricted to the university. I made it a rule for myself to accept all invitations to talk about these topics to committees concerned with these questions, to public groups, or to the media—an exercise that was time-consuming, and increasingly so in the wake of the Asilomar conference in 1975, after which the debate on gene technology began in earnest. I not only waited for invitations to speak, but, together with a group of colleagues, tried to access high school teachers and to organize seminars, courses, and eventually labs for them.

All this belongs in the realm of genetics, as seen in a wider sense. Is there a limit to the topics on which a professor is entitled to speak in public? This question was brought before me, when I did not confine my lectures on radiation damage to DNA, but also included considerations of the economic and ecologic consequences of nuclear reactors.

These questions took on an evermore urgent appeal when I joined colleagues to speak publicly about the dangers of atomic weapons and the arms race, much like the Union of Concerned Scientists in the United States or the Scientists Against Nuclear Arms in the United Kingdom. Our aim was to raise awareness among otherwise busy scientists about the problems of an ever-accelerating arms race and the ensuing destabilization among scientists.

For a while, we were quite successful. We organized a national scientists' congress on these matters in 1983, followed by an international congress in 1986, which saw the massive participation of scientists from Europe, the United States, and the Soviet Union, and at each occasion the audience was in excess of several thousand. Throughout these years, the problems of the arms race were, for a time, really a matter of discussion among scientists, including many who would otherwise refrain from involving themselves in politics. Understandably, these activities declined after the end of the Cold War.

Was all this of any avail? In terms of immediate results, the answer is certainly no. I still think, however, that such activities are more than justified. Take, for example, Germany.

[6]Space does not allow me to describe this work in detail, and a short enumeration would be boring. It has been reviewed (13). However, I want to say that work with many graduate students and postdoctoral fellows both from Germany and from abroad was very rewarding for me both personally and scientifically and I want to express my gratitude to them for their very good work and for many hours of discussion, of which I learned much and of which, I hope, they also learned something.

Nowadays, the general population is inclined toward the peaceful resolution of conflicts and is certainly against war (so much so that this is sometimes criticized in other countries). The situation was very different, however, before the First World War, when the youth of several European countries, and certainly of Germany, longed for a war that would give them the opportunity to put their heroism on display. We do not know how these changes in attitude come about, but certainly not without many people voicing them in public.

Of course we were questioned, and we also questioned ourselves, as to our legitimacy to speak on such topics really distant from our professional expertise. Those politically opposed to us denied us this legitimacy outright.

It is true that, in our role as scientists, we are very strongly asked to restrict our opinions to our area of professional expertise. For scientific progress, a highly collective enterprise, each of us is supposed to add her or his contribution, however small, with utmost care. Who, however, is then entitled to synthesize these bits and pieces? In science, this is done by respected scientists, often in the form of reviews, sometimes textbooks, and by reaching a consensus with the community, which then either accepts or rejects this synthesis. Trained in this tradition, we leave the political decisions to others. Without much asking we believe that a highly technical subject like the destabilization of the strategic situation by novel arms is treated by authors in the media in the same masterly way that physics is treated by Richard Feynman in his *Lectures on Physics* or molecular biology by Jim Watson in his *Molecular Biology of the Gene*.

Ultimately, the community that accepts or rejects their conclusions is the citizenry. This is a group, to which we, the scientists, also belong. And at the very least it is incumbent on those of us who possess an established position like a tenured professorship to cut out from our busy schedule the time to think about these matters. This is a privilege not shared by all other citizens. I think we should use this privilege and join those who scrutinize what is offered to us. If we do not do it, this is left to the media. The journalists certainly do not ask themselves, and also are not asked by the public, whether they have the competence to speak out on the most difficult political questions including the arms race. Without believing that our credits are any better than theirs, we should insist that, in some instances, they are not worse.

SCIENCE IN MODERN SOCIETY

Everybody will agree that science (and recently also biology) is shaping our material world to a great extent. Is it also influencing the way in which our society looks at this world? Here I am not so sure.

When we read about the sciences in the public media or follow the pronouncements of politicians (and here I speak mainly about Germany), the discussion is usually about the question of whether the science departments in the universities have close enough ties to the economy, whether they churn out a sufficient number of patents, and whether they train their students in a way most suitable for their future employment in industry. There is no question that all of these are important goals. Are they sufficient, though? Isn't it also the task of the natural sciences, as of all other branches of the universities, to participate in the intellectual debates of our times, in shaping the way in which we look at the world at large?

The natural sciences, as opposed to the humanities, are not the most vociferous participants in these debates. Other fields, from sociology to psychology (not to mention the arts or religion), are much more prone to explain to all of us how to look at the world. Often the spokesmen of the humanities are even telling us what our science is all about.

Surely we have learned a lot from the cultural sciences. We are all aware now that the sciences do not (only) stem from the pursuit of our curiosity about the outer and inner world. We know that other human characteristics, like ambition and greed, also come into play. They also tell us that the way we speak about what we do is most influential in shaping our understanding

of the world and that, consequently, no deep understanding of the world is possible unless philosophers and linguists have found the right metaphors that guide us in our explorations.

Important as this is, we must not forget that not everything is the result of a way of speaking, and that our understanding of the world is not (only) dictated by discourse and majority opinion, but also by the properties of the world outside. There is a world outside of us, and although we cannot see and understand it, but through our senses and through our brains, we must never forget that the world outside is shaping our interaction with and our understanding of it, and that we are not free to speak and think as we like. To remind our colleagues in the humanities of this is the task of all natural scientists.

A particularly important question to mention in this context is ethics. Very often we hear and read that scientists are the "doers," often rather blind and single-minded, and that the professionals of philosophy, especially of ethics, have to restrain the most exuberant actions of the former. I do not believe that this claim (which is certainly not that of the best minds of that science, but a simplified view often heard in the media and in the political debate) is justified. If ethics comprise the set of rules required for a good and just life, and if the lives of all of us are, among other parameters, also shaped by our environment, which constantly changes under the influence of the discoveries of scientists, the latter must not be excluded from considering these questions.

This is a particular point to discuss. Although not exclusively concerned with the erection of barriers to human activities, ethics has a strong inclination toward doing so. The Ten Commandments are a famous example: The "You Shall Not's" carry much more weight than the few active admonitions of the Third and the Fourth Commandments.

Should this also be so in the modern world? Science has certainly provided us with many improvements in our material lives. Without them we would be worse off, and some of them are indispensable to the future existence of mankind. I need only mention the impact of science on agriculture, from the introduction of artificial fertilizer in Justus von Liebig's times in the nineteenth century to the "green revolution" of the twentieth. It is possible that future generations will take a similar view of scientific achievements of the twenty-first century. If this is so, it becomes the overwhelming duty of ethics not only to inhibit wrongdoing, but also to show where the omission of doing something becomes reproachable.

If this is so, we must not only deliberate how to restrict harmful actions, but also the costs incurred, should we fail to do what is becoming possible for us. I am not saying that scientists are the only, or even the best, people to decide this. However, I equally strongly believe that they must be involved in this debate. To do so, we must first work toward a climate in the general debate where the division is not between the "doers" and the "ethicists," but between the proponents of different courses of action.

Why is this not yet so? In my opinion, too many scientists refrain from such debates. Nobody forbids that they participate. However, the very nature of science, where it is not sufficient to think well, but where each thought must be checked against nature by means of painstaking experiments, occupies so much of our daily activities and often of our nightly thoughts that not enough time is left for anything else. Still, it would be good if many of us set aside sufficient time for these considerations because shaping the opinion of an educated public is greatly important, as the debate about genetically modified organisms in agriculture has so amply demonstrated.

However, there may be a deeper reason for the often-heard belief that scientists should do their work and otherwise remain silent. The distrust of the "doers" may be deeply ingrained in the human mind. After all, it was the yielding to the temptation to eat from the tree of knowledge that led to the expulsion of Adam and Eve from paradise. In ancient Greek mythology, the blacksmith of the Gods, Hephaistos, lived deep under the earth with the Cyclopes, as did his Germanic counterpart, Alberich, who

took shelter with his dwarfs beneath the Rhine river. It seems that people, as witnessed in their sagas, harbor a deep distrust of change wrought by skilled hands and investigative minds.

This, however, should not discourage us. Despite these prejudices, science has advanced over the centuries and has bestowed on us many gifts, from modern agriculture, so vital in the fight against starvation, to antibiotics, curbing to a large extent the onslaught of infectious diseases. This shows that even ingrained prejudices can be and have been overcome successfully, and I think it is our task as scientists not to shrink back from this and to recognize the responsibility to participate in the great intellectual debates of our time.

LOOKING BACK. . .

Looking back at these 50 years of molecular biology, one cannot but be impressed. We now know much about the ways in which DNA is transcribed, RNA is processed, mRNA is translated, and all of these processes are regulated. We also know much about the necessary enzymes, etc., used in these processes and the proteins that are all encoded by their proper genes.

However, genetics is older and initially was not a science about the biochemistry of macromolecular biosyntheses. In its beginnings, it was the description of traits (later named phenotypes) due to the presence of factors (later named genes) that in either of two allelic states caused different phenotypes. The first years after the rediscovery of Mendel's work confirmed this concept in an impressive way.

Soon, however, there were difficulties. Did one gene make one phenotype or several? Was a phenotype caused by one gene or by many? Were the phenotypes caused solely by the genes, or did the environment play a role?

The attempt to answer these questions led to many auxiliary concepts without leading to a satisfactory unified picture. There was polygeny and pleioptropy, there were suppression and epistasis, there was penetrance and there was quantitative genetics as opposed to single gene inheritance. Did we then understand how the gene "makes" its phenotype? Do we know this today?

Let us consider some of the phenotypes for which genes are reported nowadays not only in the lay press, but also in the scientific literature. There is talk about the gene "for" male homosexuality, "for" female breast cancer, and "for" the obesity that haunts both sexes. It is clear by now that the gene is not a direct cause of these phenotypes. It is linked to them via several steps by what philosophers call a "chain of causes." However, the farther we move down this chain of causes, the more we are forced to acknowledge that other causes come into play, too. It is like the pedigree of Abraham in Genesis. There are nine generations between Shem and Abraham. Could we say that Shem was the progenitor of Abraham? He certainly was one, but there must have been 511 others, of whom we hear little. Still, the character of Abraham must have been influenced by them as well as by the known progenitor Shem.

The language in which we describe the relation between a gene and a distant phenotype is deceptive. It prompts us to assume that the first is the cause of the latter rather than a contributing factor[7]. All the discussions about a difference between single gene inheritance and quantitative genetics, all the disappointments if one group discovers a gene "for" schizophrenia linked to one chromosome and another group has similar findings for another chromosome, and all the quarrels about "Nature versus Nurture" become meaningless if we acknowledge

[7] The absurdity of this becomes apparent if we try to use such language in everyday life. Imagine a man who is in trouble with his beloved girl, and he knows that he has to write to her and apologize. He cannot do so, however, because his pencil is broken, and to his dismay he discovers that his pencil sharpener does not work. The letter is not written and the girl takes her phone and rings another person to console herself. If we do not know this story completely, if we only see the broken pencil sharpener and the reaction of the girl, and if we are trained in the tradition of genetic nomenclature, we might call the broken gadget the suppressor of true love. Ridiculous as this sounds, that is exactly what geneticists do every day!

the role of the gene as one actor among many for the distant phenotype, and if the only direct phenotype is the RNA, the sequence of which is encoded in the gene.

It might be better not to talk about cause and effect, but rather about interactions (like the physicists do), mostly between two players. The gene interacts with the transcription apparatus, and the result is an RNA that may or may not be altered either by a mutation in the DNA sequence or by an alteration of the transcriptase, causing faulty transcription.

This will sound to many as sheer word playing, philosophy at best (and scientists are often not fond of philosophy and use the word in a rather derogatory sense). However, if we take this suggestion seriously, many of the concepts elaborated by geneticists in the first half of the last century cease to be puzzling. No longer is it necessary to discuss at great length the proposition that a gene causes a certain result not with certainty but only with probability. The gene does its work and acts as an information-carrying template in transcription. But when we look at a trait, it may be removed from the gene that we investigate by several steps (splicing, translation, protein action, cellular events), and moreover, many genes may participate in all of these steps. Therefore, it need not disturb us when the final outcome, depending on so many other interactions, is different in different individuals, because the probability of differences between members of a group even of limited size increases strongly with the number of genes playing a role. The description of a particular gene having a certain effect with only a limited probability is then understandable.

There is no longer a reason to distinguish between a normal gene and a quantitative trait locus (which accounts for only part of the variance of this trait within a population). Both of them produce their RNA, and it is only the role of this RNA and of its subsequent products that differ among different genes. If, in a complicated chain of reactions, a particular RNA and the protein made from it have only a small modifying effect on the eventual outcome, the gene is said to have a minor quantitative effect. At the level of the gene, however, a deletion of this gene is not different from any other.

The acknowledgment of such a distinction between a direct interaction of two players from the eventual, unpredictable outcome of this should not only influence our thinking about genetics, but can reach even further. Nowadays, it has become popular to hold people, and in particular scientists responsible for distant consequences. Otto Hahn is said to be responsible for the atom bomb, and once I heard, in a parliamentary committee, the seriously posed question of whether the federal government could guarantee that genetically manipulated crops, even if benign by present standards, would not cause harmful evolutionary alterations a few hundred years hence.

In my opinion, we should refrain from such ideas because they reach beyond our capabilities. The decision to once and for all refrain from scientific activities that could be harmful for mankind in an unforeseeable and unknown future must lead to complete inactivity, and this would be counterproductive. On the other hand, we should watch the outcome of our work carefully. Should a dangerous development become discernible, we, as the scientists, should be the first to spot it and to alert the public about it (as has often been the case in the second half of the last century, e.g., in the Asilomar conference in 1975, where scientists themselves first discussed the possibility of dangers of the newly emerging gene technology!).

. . .AND LOOKING AHEAD

This is certainly more difficult than evaluating the events of the past. Should one still try a little step in this direction? I will do so and hopefully not become either too lengthy or too speculative.

We hear much about the overwhelming role of the genes in biology these days. Genes are said to carry the blueprint of the organism, to possess all of the information to explain life. Sequencing the genome and finding out about all of the genes in it should, as we sometimes read, reveal the way in which organisms develop

and function. Is this a reasonable expectation? I have my doubts.

The study of the genomic sequences has already produced many surprises, among them the finding that the number of genes is smaller than expected, and is, in human beings, not much larger than in much simpler organisms, like the nematode *Caenorhabditis elegans* or the crucifer *Arabidopsis thaliana*. Similarly interesting is the observation that a large number of the genes, including many that encode proteins of most important and basic functions, are very old, dating back to a time when eucaryotes had not yet split from either eu- or archaebacteria. Still, it cannot be denied that recent mammals, including man, are very different from bacteria. Do we really expect genes to make us mammalian or even human?

Another puzzle: While the concept of pleiotropy, the involvement of a gene in seemingly unrelated functions, is old, the involvement of the same gene products in a plethora of functions has by now become overwhelming. The advent of the microarray techniques has shown that the addition or deletion of a single gene involved in a developmental process can have an influence on the expression of hundreds, if not thousands, of other genes.

If a single process, e.g., eye formation, needs a very large fraction of all genes, and if the number of genes is smaller than previously thought, what do we have to think about for the relation of the genes to the phenotypes?

I suggest that already at the level of cells, and more so at the level of whole organs or of organisms, new forms of complex organization with new, emergent properties will be found. In these complex organizations determining certain levels of life the genes will be building blocks for regulatory modules.

Is such a suggestion amounting to the claim that life is not based on the functions of the genes? Certainly not! I illustrate my view by discussing the relation of nucleotides to genes. Is it conceivable to have a gene without the constituent nucleotides? No! Is it conceivable to alter an important biological trait by exchanging a single one of these nucleotides in a certain sequence? Obviously yes! Is it then reasonable to say that a certain trait, say sickle cell anemia, is caused by the T now present instead of an A at a particular position in the mRNA for the ß-chain of globin? This would hardly be claimed by a geneticist. Are we surprised that, given the absolute importance of the nucleotides for the structure of the genes, there are only four of them? Not at all. With these four nucleotides it is possible to build an unlimited number of sequences, of which many contain the information for a biologically important RNA, often a mRNA. The information is the new, emerging property, making use of the relations of many nucleotides to each other, that distinguishes a gene from an ensemble of nucleotides.

By this way of thinking, the nucleotides do not lose their importance, but this importance lies, in the example mentioned above, in their being part of a larger ensemble of them, namely the gene. The role of the nucleotide in this instance could not be guessed from any of the properties of the molecule looked at in isolation. Its role as determining a codon within a gene is a new, emerging property.

I think it is possible that one day, perhaps in the not too distant future, scientists will describe networks of proteins, many of them regulatory, others with enzymatic, transport, or structural functions, all being expressed at particular places and at specific times. They will unravel the function of cells, and later of whole organs. The genes necessary for the formation of these proteins will be numerous, and they will show up again and again in the different networks to be found and analyzed. Their role in a particular module, with its emerging properties, will not be predictable from the most thorough analysis of its sequence.

If these ideas have any merit, there must be an important difference between the genes as building blocks of higher-order networks and the nucleotides as building blocks of genes. There are only four nucleotides and none of them have alleles compatible with life and, thus, do not allow Darwinian evolution. It will also be impossible to find a gene lacking one of these. Even if there were such a gene in a particular

organism, we would not find a mutant removing one nucleotide from the makeup of genes, because the many other genes could not be made and life would immediately collapse.

With genes, the situation is different. There are many more of them, and many of them will be involved in many biological functions, and therefore will be indispensable. Even the relatively simple production of an enzyme depends not only on the gene encoding the information for its sequence, but also on the genes for the whole transcription-translation machinery, and others not enumerated here. Most of them will belong to the indispensable class, the mutations of which will be early lethals and will, for this reason, never show up in a genetic analysis of this particular enzyme. The gene, however, which carries the sequence information for the enzyme, will undergo discernible mutations, as will some genes involved in the regulation of this particular synthesis.

Looking this way, the genes discovered by genetic analysis of (nonlethal!) mutants will not be the most important ones for a particular function, but rather the ones most easily discovered (and by that property possibly of only limited general importance for the cell, though of great value to breeders!).

The constitution of the networks will be unraveled by, e.g., microarray techniques, which are able to show the proteins and the genes involved without mutating or deleting them.

In genetics, the new concept of information is the key to understanding. The chemical and base-pairing properties of nucleotides play only a minor role when genetic information is discussed. In a similar manner, the discussion of the properties of genes may be delegated to the background when higher-order networks are investigated. These will probably be discussed in a novel language yet to be developed. The properties of the genes, will, when necessary, be looked up in data bases, which by then will hopefully be very comprehensive.

Although the study of genetics proper will certainly not end, the main concepts to be gathered from this science may already be at hand, and new vistas will open the view in a new world of biology, which may be similarly adventurous for a new generation of biologists, as the molecular biology of the gene was in the second half of the twentieth century for my generation. I can only express my hope that they will have the same opportunities and the same exhilaration using them that my generation was privileged enough to enjoy.

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