Perspectives

Anecdotal, Historical And Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Quarreling Geneticists and a Diplomat

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IN the 1950s the hydrogen bomb was new; it was also fearsome. Some of the test explosions produced debris that was dispersed by high-altitude winds, dropping radioactive fallout over an entire hemisphere. Some geneticists feared that mutations induced by the radiation would constitute a significant genetic hazard to future generations. Other people argued that the tests were a necessary part of the Cold War. Above-ground testing became a divisive political issue and played a large role in the presidential campaign between DWIGHT EISENHOWER and ADLAI STEVENSON, STEVENSON calling for cessation.

Responding to calls for a scientific evaluation, the President of the National Academy of Sciences, D. W. BRONK, appointed six committees to study the question. Collectively they were called the Committee on Biological Effects of Atomic Radiations (BEAR). Because of the very low individual doses, most effects of the fallout were thought to be unimportant. Cancer risks were not regarded as significant, because at that time it was generally assumed that somatic effects, cancer in particular, occurred only above a threshold dose much higher than any individual would receive from peacetime nuclear applications. In contrast, geneticists believed that each dose, however small, carried a correspondingly small but nevertheless real risk of mutation induction. And a tiny dose to billions of people added up to an enormous number of ionizations.

The genetics committee included some of the best known geneticists of the classical period: MULLER, WRIGHT, STURTEVANT, BEADLE, DEMEREC, SONNEBORN, and LITTLE.[1] Human genetics was represented by JIM NEEL, who was studying the children of the bomb survivors in Hiroshima and Nagasaki. BILL RUSSELL, from Oak Ridge, brought the latest information from his megamouse experiments. BENTLEY GLASS, as rapporteur, had the tedious job of taking notes. A man with the patience of JOB, he only once asserted his independence and asked for an adjournment to ease his writer's cramp.

In what at first appeared to be a strange decision, BRONK appointed as chairman of the genetics committee, not a geneticist but a mathematician, WARREN WEAVER. The decision turned out to be providential. After a distinguished mathematical career at the University of Wisconsin, WEAVER had joined the Rockefeller Foundation in 1928, becoming director for natural sciences in 1932 and remaining in this position until 1959. He had an enormous influence on the direction of biological research. One of his early decisions was to shift Rockefeller funds away from the physical sciences and toward biology, particularly those areas that made the greatest use of physics, chemistry, and mathematics. He was quick to recognized the importance of FLEMING's discovery that the mold Penicillium had antibiotic properties, and he vigorously supported FLOREY and CHAIN in the isolation and purification of penicillin. He also supported the war-time search for mutations that increased yields and the development of techniques to produce penicillin on a large scale. In the words of GLASS (1991), "If the Rockefeller Foundation had done nothing more in its entire first century than support the inauguration of the age of antibiotics in medicine, would that not be enough to justify its record of humanitarian accomplishments?" For a follow-up discussion on bacterial resistance to antibiotics, see DAVIES (1995).

Another example of WEAVER's foresight was the decision to support LINUS PAULING in his work on structural chemistry. WEAVER recognized PAULING's genius and the future biological possibilities from his discoveries. He also supported the work of BEADLE and TATUM in the development of biochemical genetics in Neurospora. In fact, this project would have been closed down during the war years were it not for WEAVER's backing. And not least, in 1938 he coined the expression "molecular biology." In his own view, nothing that he did was

[1] The members of the Genetics Committee were: WARREN WEAVER (Chairman), H. BENTLEY GLASS (Rapporteur), GEORGE W. BEADLE, JAMES F. CROW, M. DEMEREC, G. FAILLA, ALEXANDER HOLLAENDER, B. P. KAUFMANN, C. C. LITTLE, H. J. MULLER, JAMES V. NEEL, W. L. RUSSELL, T. M. SONNEBORN, A. H. STURTEVANT, SHIELDS WARREN, and SEWALL WRIGHT. CHARLES COTTERMAN was appointed but was an early dropout.

as important as realizing the importance of the structure and properties of large biological molecules and supporting research in this area. Even though few knew its origin, molecular biology became not just a catchword, but a guide to the kind of thinking that led to the molecular revolution. The Rockefeller Foundation provided financial support for the BEAR Committee.

WEAVER turned out to be a magnificent chairman, steering a group of contentious geneticists through their rancorous disputes to a consensus, all with the skill worthy of a TALLEYRAND. According to GLASS (1991), "Weaver's contribution to this momentous scientific report remains, I believe, the very greatest scientific contribution of his own life." Surely this was *one* of his greatest, although my vote for *the* greatest accomplishment goes to his early realization of the importance of molecular biology and coining the expression.

The first BEAR Committee meeting took place at Princeton University in November, 1955, and after several more meetings, the report was published in June, 1956 (BEAR 1956). In the early stages, the Committee leaned heavily on the advice of H. J. MULLER. MULLER, in his earliest papers describing X-ray production of mutations, had cautioned against any unnecessary radiation that might reach the germ cells. The principles that were established by 1955, mostly from Drosophila research, were as follows: the overwhelming proportion of mutations whose effects can be detected are harmful; ionizing radiation enhances the mutation rate; most "recessive" mutations are partially dominant; the effect is independent of dose rate; and the number of mutations produced is strictly proportional to the dose, so that there is no "safe" dose. Thus, to MULLER, the total dose to germ-line cells during the pre-reproductive years was all that mattered. Dose-rate dependence was not discovered until after the report was published, and of course, such things as repair mechanisms were not known. Tissue, cell, and sex differences were largely unexplored. In 1956 the problem appeared simpler than it did later, or does now, for that matter.

The amount of radiation required to produce a number of mutations equal to those that occur spontaneously (the doubling dose) was estimated at 5–150 roentgens (r). (In those days radiation was measured in roentgens and rems, rather than the 100-fold greater current units, grays and sieverts.) The doubling dose could hardly be less than 5 r, for the estimated average radiation received in the first 30 years of life from natural sources (cosmic and ground radiation) was estimated as 4–5 r. A doubling dose this low would imply that all mutations are caused by natural radiation. This was known not to be the case in Drosophila, and there was indirect evidence for its not being true in humans either. The Committee consensus was that the value probably lay between 30 and 80 r, based mostly on comparison of radiation-induced rates at selected loci in the mouse with crude estimates of spontaneous rates in humans. It had recently been discovered that the induced mutation rate per roentgen was considerably higher in the mouse than in Drosophila, and some had worried that the human rate might be still higher. The data on possible indicators of mutations among children in Hiroshima and Nagasaki were not statistically significant, but could be used to set an upper limit on human susceptibility. They provided some assurance that human genes are not grossly more mutable than those of mice.

On all this the Genetics Committee members were in essential agreement. The division arose over a desire to be quantitative about the societal impact of an increased mutation rate. MULLER (1950) was deeply impressed by the principle, first enunciated by HALDANE (1937), that each mutation, however mild, has the same average effect on the fitness of the population. The reason is that mild mutations persist more generations in the population and affect a correspondingly larger number of individuals. In MULLER's terminology, each mutation in a stable population leads to one gene extinction, or "genetic death;" in a growing population the number is correspondingly larger. He realized that recessiveness and, especially, epistasis could reduce the impact, since several mutations could be picked off in a single genetic death. But he did not think that this would make a substantial change; the current emphasis on truncation selection as a load-reducing mechanism was not part of the thinking in those days. MULLER argued forcefully that the genetic death principle was the only way to get at the total impact of a mutation; to measure only tangible effects was to ignore the submerged part of the iceberg. Here is a description of the concept, in WEAVER's lucid prose: "One way of thinking about this problem of genetic damage is to assume that all kinds of mutations on the average produce equivalent damage, whether as a drastic effect on one individual who leaves no descendants because of this damage, or a wider effect on many. Under this view, the total damage is measured by the number of mutations induced by a given increase in radiation, this number to be multiplied in one's mind by the average damage from a typical mutation."

Strong objections to this came from WRIGHT. He argued, and most Committee members agreed with him, that it is not meaningful to equate all genetic deaths. A mutation causing early embryonic death or failure to reproduce could have no appreciable effect on human welfare, in contrast to one causing a severe physical or mental impairment that could have devastating effects on both the individual and the family. Yet each leads to one genetic death.

Furthermore, WRIGHT said, a natural population contains many isoalleles, indistinguishable by ordinary means, and each having an extremely minute effect.

Such alleles were the stuff of human quantitative traits, he argued, and most such traits had an intermediate value as the fitness optimum. Too much or too little of almost anything is bad, he said. At that time the existence of molecular polymorphism at many loci was not known, but WRIGHT was confident that this would one day be revealed. In emphasizing nearly neutral isoalleles, WRIGHT anticipated the "infinite allele model" (KIMURA 1983), which later played such a large part in discussions of molecular polymorphism. Furthermore, WRIGHT emphasized that the HALDANE-MULLER principle did not apply to heterotic and frequency-dependent loci. Thus, the fraction of deleterious mutations might not be nearly as high as MULLER argued. And, as was his wont, WRIGHT provided a detailed analysis, full of equations.

STURTEVANT for the most part sided with MULLER. In particular, he did not like WRIGHT's analysis. STURTEVANT argued that, although indistinguishable isoalleles may well constitute a large part of the genetic variability of natural populations and be of great importance for human welfare and for evolution, they were not the kinds of mutations observed in radiation experiments in Drosophila and mice, which provided the basis for the Committee estimates. He also noted that STADLER had provided evidence that ionizing radiation produces mainly deletions and other products of broken chromosomes. In this regard he differed from MULLER, who had maintained that radiation more or less mimicked spontaneous mutations. Viewed through a 1995 retrospectroscope, STURTEVANT's view looks very good, the best of the three. In any case, the view that mutations were harmful prevailed in the Committee. The report was careful to say, however, that among mutations *with a detectable effect,* the overwhelming majority are harmful. This seemed to gain everyone's acquiescence, if not enthusiastic approval.

This difference was largely reconciled, at least as far as the wording of the report was concerned. But the biggest stumbling block remained. The argument was over genetic deaths and the applicability of the HALDANE-MULLER principle. And MULLER and WRIGHT dug in their heels. (Since I had been associated with both MULLER and WRIGHT and was familiar with their views, my role was to explain these to WEAVER, who, needless to say, was a quick study. I am sure he found the mathematical arguments quite elementary, but he liked the elegance and simplicity of the HALDANE-MULLER principle.) MULLER argued vehemently that his was the only way to assess the total impact; the uncertainties of interpreting genetic deaths in terms of human suffering, he said, were not as fatal as dealing with only tangible effects and sweeping the uncertainties under the rug. MULLER was both stubborn and forceful. He oversimplified, he overstated, and he brought up every possible argument. As he argued, I kept thinking what a great trial lawyer he would have been. But as a politician, he was far less effective. He never learned that argumentative overkill is not the best way to win converts.

WRIGHT was no less stubborn, and he was longer-winded. He stressed the importance of isoalleles, heterosis, and intermediate optima. He talked at enormous length, arguing, sometimes repetitively, that we must try to make distinctions among the different phenotypic effects of mutations as to their societal impact. He classified people by their cost to society and their contribution. Most people, he said, cost society little and contribute little. Others, such as professionals, cost society a great deal in education and high living standard, but also contribute substantially. Some people make great contributions with little cost—selfless individuals with a social conscience. Others cost heavily, but contribute little—charlatans, criminals, inheritors of wealth. And so on. He tried to determine which classes have a significant mutational component. WRIGHT's seemingly endless monologues did not please everybody. During one of them STURTEVANT whispered to me, "What would it be like if there were two WRIGHTS?"

Only a few days before the release date for the report, MULLER objected violently to a paragraph that had been put in to please WRIGHT, and said he would not sign the report if these sentences were included. At this point WEAVER's diplomatic skills again came into play. He wrote a statement giving both views, softening each somewhat, and in a long telephone conversation persuaded MULLER to accept it. Then he was fearful that WRIGHT might not go along and sent a letter to me (WRIGHT and I worked in the same building and saw each other daily), which I here reproduce.

June 8, 1956

PERSONAL AND CONFIDENTIAL

Dear Jim:

I am sending you herewith a copy of the material which is replacing pages 14 and 15 of the report. It has not been changed since I read it to you on the telephone. I was simply horrified to receive yesterday a telegram from Muller stating that he was unwilling to sign the report if it included "Wright's paragraph alleging great differences in total damage per mutation or its equivalent."

I am taking the position that it would be a scientific and social tragedy if this report cannot receive the unanimous backing of the group. It would create an absolutely false impression, and it would be in fact really ridiculous, if any member fails to stand by the report at this stage because of disagreement over some relatively minor aspect.

I am mailing to Professor Wright a copy of the new version of pages 14 and 15, with a very short note saying that I hope he is reasonably happy with it. I am writing this confidential letter to you so that you will know the background if, by any foul chance, Professor Wright should be disturbed over the way in which I rewrote and

incorporated this material. If that happens you could make clear to him that I went just as far as I possibly could, for I talked with Muller on the phone yesterday afternoon, and by reading him this actual version and arguing with him, I have gotten him to agree to accept it. I don't think that he would accept anything that is anything closer to Wright's original wording.

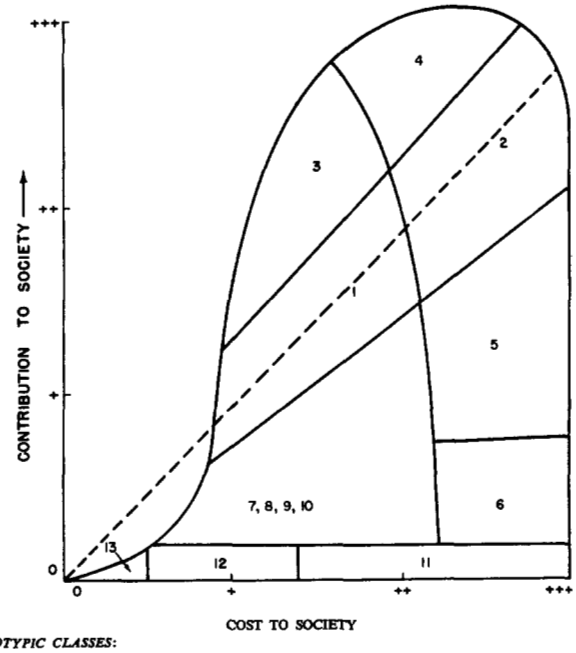
Very sincerely yours,
Warren Weaver

Although he wasn't entirely happy, WRIGHT was willing to go along and I so informed WEAVER. At last, only days before its release date, the report finally carried a unanimous endorsement, to the relief of the Committee members, the National Academy of Sciences, and especially WEAVER. For those who are curious, WEAVER's words may be found in section (7) of the report (BEAR 1956), starting on page 17.

Yet there is a supreme irony. The whole rancorous debate had no effect on the specific recommendations. The Committee recommended: "Keep the dose as low as you can." It used the natural background radiation level, thought to be about 4–5 r per 30-year generation, as the quantitative standard. It recommended that a uniform national standard for man-made radiation be such that the average accumulated gonadal dose from conception to age 30 be less than 10 r. At the time the Committee thought that about half this amount would come from medical radiation, mostly diagnostic. (Therapeutic radiation, although given in much greater individual amounts, produces less genetically significant radiation to the population.) The amount from fallout was much less. The Committee estimated that if weapons testing continued at the current rate, the genetic dose from this source would be less than 0.1 r. Nevertheless, a very small amount of individual radiation from bomb testing, since it spread over much of the world, affected an enormous number of people. Curiously, a study designed to consider the effect of bomb testing ended up showing a much greater contribution from medical radiation. As a result, a number of radiation-reducing procedures were introduced into the practice of diagnostic radiology and are now standard.

The general viewpoint of the Committee members was that, since mankind has survived millions of years with background radiation, increases of the same magnitude are not likely to have any disastrous effect. Furthermore, if the doubling dose is 30–80 r, the increase from 10 r would be a small fraction of the spontaneous rate. In WEAVER's words, the 10 r limit is "reasonable (not harmless, mind you, but reasonable)." The entire genetics section was written in WEAVER's informal, easy to read, conversational style, and I believe that a large part of its quick acceptance and influence is owed to this.

The recommendations were quickly adopted by the National Committee on Radiation Protection and soon



PHENOTYPIC CLASSES:

1. Contribution = cost at low level
2. Contribution = cost at high level
3. Contribution > cost at low level
4. Contribution > cost at high level
5. Contribution < cost because of unearned wealth, etc. (playboy type)
6. Contribution < cost because of antisocial career
7. Contribution < cost because of subnormal physical constitution
8. Contribution < cost because of subnormal mentality
9. Contribution < cost because of interruption of career by physical breakdown
10. Contribution < cost because of interruption of career by mental breakdown
11. No contribution, high cost because of complete incapacity from childhood (long life)
12. No contribution, moderate cost because of death before maturity
13. No contribution, little cost because of pre- or perinatal death

FIGURE 1.—WRIGHT's societal contribution-cost analysis.

became the basis for national policy. The major innovation was to regard the population average as the controlling consideration. Previously, all radiation protection standards had been based on observed somatic harm to the individual, and therefore involved much higher doses. The National Academy of Sciences at that time had not done this kind of policy-setting report. It has done many since, but this one was outstanding in the way it immediately and permanently changed public policy in radiation protection. Since that time there have been studies by the United Nations, the National Council on Radiation Protection and Measurements, the International Committee on Radiation Protection, and the National Academy of Sciences. These are much more detailed, but have not caused a major change in public policy, although acceptable radiation dosages continued to decrease.

What happened to the material that WRIGHT wrote? After 1956, the Committee continued under the chairmanship of BEADLE and with the addition of TH. DOBZHANSKY, who added his debating skills to WRIGHT's arguments. The old divisiveness reappeared. WRIGHT had reworked his analysis and it finally appeared in a second report (BEAR 1960). But whereas the first report (BEAR 1956) was front-page news and widely discussed, the second one passed largely unnoticed and WRIGHT's analysis was buried with it.

WRIGHT's analysis is reproduced here as Figure 1. For the purpose of a societal analysis, he classified people into 13 groups. With typical breadth and thoroughness, he tried to classify phenotypes on the basis of cost and benefit, cost to society *vs.* contribution to society. For most of the population these approximately balance, around the 45° line (provided that society is static; overall improvements would raise the slope). WRIGHT concluded that categories 7–13, in which the costs to society outweigh the benefits, all have a significant genetic component. But he was careful to say that the contribution of mutation to the incidence remains in much doubt, as of course it still does. It is easy to understand that, although this was regarded as a thoughtful analysis, the Committee members generally agreed that it was not needed in the report. It was included as an appendix. JIM NEEL was also on the committee and has written about some of his memories of both reports (NEEL 1994).

A 35-year retrospective look at WRIGHT's diagram is revealing. From the present, when the emphasis is on people's entitlements from society and not on their obligations, it is refreshing to look back on WRIGHT's unabashed balancing of people's contributions to society against their costs. As far as I know, WRIGHT never discussed this again, but it epitomizes his way of thinking.

Recent years have brought two major changes. Shortly after the 1956 report was issued, a new view of somatic effects began to be taken seriously. It was argued by several—E. B. LEWIS, of *Bithorax* fame, was particularly effective—that malignancies may, like mutations, have no threshold. Hence the assumption of linearity at low doses, down to dose zero, began to be applied to cancer risks. Since this affects the current population, not descendants who may be several generations removed, it soon became the item of major concern. Policy debates over radiation protection standards now center mainly on assessment of somatic risks.

The second change concerns chemical mutagens. The BEAR Committee did not consider chemicals. This may seem surprising, in view of the fact that AUERBACH's discovery of the mutagenicity of mustard gas was already well known (BEALE 1993). MULLER regarded any discussion of chemical mutagenesis as likely to dilute his efforts to protect the public from radiation effects. A second and more important reason was that at that time the only known chemical mutagens were highly toxic substances, like mustard gas. Any public exposure would be accidental (or a possible consequence of war). It was several years later, after microbial and molecular techniques became much better, that geneticists found all sorts of compounds that were highly mutagenic, yet not overtly toxic. The 1960 report did discuss chemical mutagens, but they did not receive the emphasis that they would later, when they largely displaced radiation as a matter for health concern.

MULLER didn't have his way with much of the wording of the Committee report. But his major practical recommendation—that the standard be set low, in the vicinity of the natural background level, and that it be based on a population average, not an individual dose—prevailed. In the years immediately following the BEAR report there were numerous discussions, committees, and Congressional hearings. PAULING joined MULLER and was a forceful advocate. Radiation protection became a major concern and, among other consequences, above-ground bomb testing was ended. MULLER certainly won the day. In my view, he and PAULING, along with others much less visible (including me), oversold the dangers and should accept some blame for what now seems, to me at least, to be an irrational emphasis by the general public and some regulatory agencies on low-level radiation in comparison to greater risks.

The National Academy of Sciences continued to issue reports periodically. As information accumulated, the reports were modified. The approach (*e.g.*, BEIR 1972) was that of neither MULLER nor WRIGHT. Like WRIGHT, the Committee dealt with phenotypes and emphasized effects on early generations, rather than counting genetic deaths as MULLER had advocated. But the phenotypes were classified by assumed mode of inheritance, with no attempt to quantify societal costs and benefits. Assuming a doubling dose of 20–200 rem, based mainly on mouse data, the 1972 Committee estimated the first generation and equilibrium numbers of affected persons in a population of one million exposed to 5 rem per generation. The traits were classified as dominant, recessive, *X*-linked, cytogenetic, physical anomalies, and constitutional and degenerative diseases. There are still no reliable data from which to estimate the human radiation-induced mutation rate. It is still necessary to depend on the mouse and on the upper confidence limits of nonsignificant human effects (NEEL 1994).

As I mentioned earlier, the 1956 report was presented at a press conference and received wide publicity. Then still another problem arose. Most of the report was technical and not controversial; only the genetics section, thanks to WEAVER, was written for the general public. Writers from the *Scientific American* were co-opted to write a popular version of the report, and they proceeded to change some of the hammered-out wording of the genetics section. WEAVER again came to the rescue, persuading these writers to leave this section largely alone, and undoubtedly averted another crisis with MULLER or WRIGHT, or both.

WEAVER had done a great job, but he had had his fill. The press conference was held on June 12, 1956 and he resigned the next day.

I should like here to acknowledge my personal indebtedness to WARREN WEAVER in another regard. The next year, on his recommendation, the Rockefeller Foundation supported me on a trip to Japan to spend the summer of 1957 working with MOTOO KIMURA.

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