Heritable Variation and Mutagenesis at Early International Congresses of Genetics

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Nothing makes sense in evolution except in light of the molecular basis of genetic stability and change.[1]

I encountered one John Walter Drake, known to most everyone as "Jan," 35 years ago in the Journal of Molecular Biology. It was in this once most fashionable journal of *avant garde* genetics that he published the first spectrum for UV-induced mutagenesis (Drake 1963). His experimental system was the *r* II region of bacteriophage T4. Comparing Jan's data with Seymour Benzer's *r* II spectrum for spontaneous mutations (Benzer 1961), it became immediately clear that the spectra, the positions of "hot spots" and the mutational specificities for UV-induced and spontaneous mutations are different. This article was the inspiration for what has become a veritable industry in contemporary analysis of mutational spectra at the genetic site and DNA sequence levels. The importance of this work was recognized immediately, particularly by photobiologists interested in the recently discovered UV photoproducts in DNA (thymine dimers). Thus Jan was invited to participate in the U.S. National Academy of Sciences–National Research Council conference on *Structural Defects in DNA and their Repair in Microorganisms*, held at the University of Chicago in October of 1965 (Haynes *et al.* 1966).[2] It was there that I first met him in person and we have remained close friends and colleagues ever since.

As readers of Genetics will know, throughout his career Jan has been one of the preeminent students of the molecular basis of mutation. Indeed he wrote what soon became, and remains almost three decades later, *the* classic book on the subject (Drake 1970). It must be a classic because it received such an effusive review in Science as soon as it was published (Haynes 1971).

Throughout his career Jan also has been an unusually good and very dedicated citizen of science. To commit oneself whole-heartedly to responsible public service in science, and also maintain one's position as a formidable researcher in a highly competitive field, is a challenge that few can handle. As Editor of Genetics he induced a macromutation in its appearance and general quality which has made it the leading international journal in its field today. Thus he has been in a unique position to know who is doing what, and doing it well, in basic genetical research worldwide. This background made him the obvious person to serve as Chairman of the International Program Committees not just for one, but for *two*, of the eight International Congresses of Genetics (ICG) that have been organized since he completed his Ph.D. in 1957: the 16th held in Toronto in 1988, and the 18th to be held in Beijing in August 1998. As President of the Toronto congress and an honorary Vice-President of the Beijing congress, I know how much thought, time and effort he contributed to formulating the scientific programs of these two large and important meetings.

Table 1 contains a list of all meetings of the ICG, their Presidents and Secretaries-General (or equivalent where known), and bibliographic references to their proceedings. Further details regarding sponsorship, attendance and numbers of papers presented at the first 16 congresses are available in the report of the Secretary-General for the 1988 congress (Walden 1989). The proceedings of the ICGs provide a fascinating overview of the problems and theories that have attracted the attention of our international community during the first century of genetics.[3]

As I reflected on topics I might discuss in Jan's *Festschrift*, it occurred to me that it would be interesting to recall some of the highlights of past ICGs. Most of the notable advances in genetics' broad domain have been

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[1] My apologies to Theodosius Dobzhansky.

[2] This was the first formal symposium on the macromolecular processes of DNA repair and its relation to mutagenesis. For an historical account of the discovery of DNA repair see Friedberg (1997).

[3] The published proceedings of genetics congresses contain a wealth of material that should be grist for the mill of any serious historian of genetics whether professional or amateur. It would be an appropriate "millennium project" for someone, perhaps a graduate student in the history of biology, to make a detailed study of all 20th century ICG proceedings in order to delineate the shifting balance of interests in the various branches of genetics at these congresses. Some good examples of the historical gems that might be mined in such a project are evident in the Presidential Addresses of Ernst Hadorn and Curt Stern at the 11th and 13th ICGs in The Hague and Berkeley, respectively (Hadorn 1965; Stern 1974), and in Crow's article on the 6th ICG held at Cornell in 1932 (Crow 1992).

TABLE 1

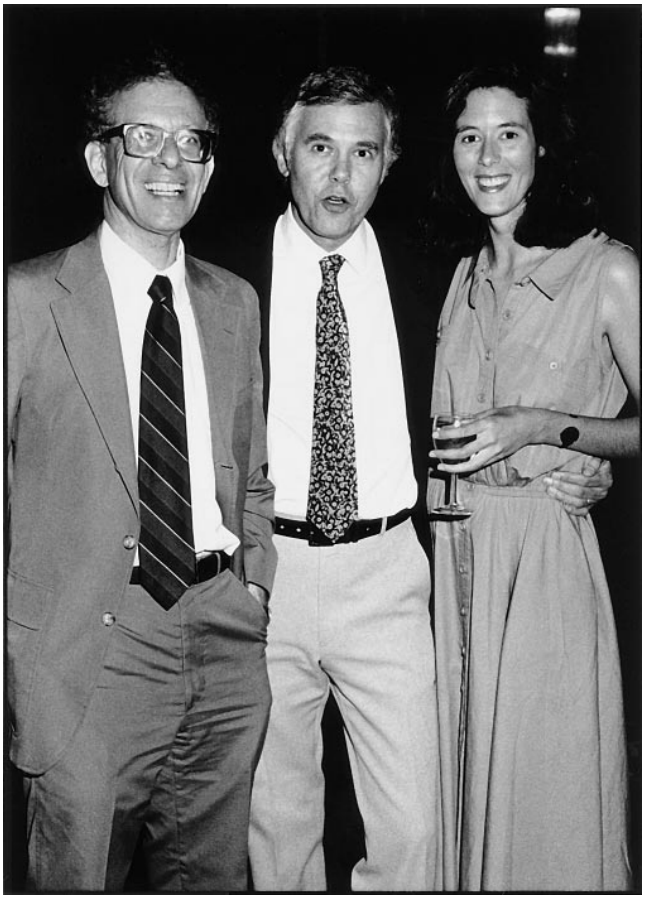
International Congresses of Genetics (ICGs)

1998: 18th ICG, **Beijing**, China. C. C. Tan/Shouyi Chen.
1993: 17th ICG, **Birmingham,** England. Ralph Riley/Derek Smith.
1988: 16th ICG, **Toronto,** Canada. Robert H. Haynes/David B. Walden.
Genome **31:** Nos. 1 and 2, 1989. Abstracts: Genome **30: suppl. 1**, 1988.
1983: 15th ICG, **New Delhi,** India. M. S. Swaminathan/V. L. Chopra.
Genetics: New Frontiers, 4 vols., Oxford and IBH Publishers, New Delhi, 1984.
1978: 14th ICG, **Moscow,** USSR. N. V. Tsitsin/D. K. Belyaev.
Vol. 1: Well-Being of Mankind and Genetics, Vol. 2: Problems in General Genetics; Vol. 3: Molecular Bases of Genetic Processes. MIR Publishers, Moscow, 1980–81.
1973: 13th ICG, **Berkeley,** CA, USA. Curt Stern/Spencer W. Brown.
Genetics **78:** No. 1, 1974; **79: suppl.**, 1975. Abstracts: Genetics **74:** June **suppl.** No. 2, Part 2, 1973.
1968: 12th ICG, **Tokyo,** Japan. Hitoshi Kihara/Yataro Tazima.
Proceedings of the XII International Congress of Genetics, Science Council of Japan, 3 vols., Tokyo, 1968–69.
1963: 11th ICG, **The Hague,** The Netherlands. Ernst Hadorn/C. L. Rümke.
Genetics Today, Proceedings of the XI International Congress of Genetics, Pergamon Press, 3 vols., Oxford, 1963–65.
1958: 10th ICG, **Montreal,** Canada. Sewall Wright/J. W. Boyes.
Proceedings of the X International Congress of Genetics, University of Toronto Press, Toronto, 1959.
1953: 9th ICG, **Bellagio,** Italy. R. B. Goldschmidt/G. Montalenti.
Proceedings of the 9th International Congress of Genetics, Caryologia **VI: suppl.**, 2 parts, 1954.
1948: 8th ICG, **Stockholm,** Sweden. H. J. Muller/G. Dahlberg.
Proceedings of the Eighth International Congress of Genetics, Hereditas, **suppl.** 1949.
1939: 7th ICG, **Edinburgh,** Scotland. F. A. E. Crew.
Proceedings of the Seventh International Genetical Congress, Cambridge University Press, Cambridge, 1941.
1932: 6th ICG, **Ithaca,** NY, USA. Thomas Hunt Morgan/R. A. Emerson.
Proceedings of the Sixth International Congress of Genetics, Brooklyn Botanical Garden, Brooklyn, NY, 1932.
1927: 5th ICG, **Berlin,** Germany. E. Bauer.
Z. f. induct. Abstamm.-u. Vererbungsl., **suppl. 1,** 1928.
1911: 4th ICG, **Paris,** France. Ives Delage/Ph. De Vilmorin.
4e Conférence internationale de génétique, Comptes Rendues et Rapports, Masson et Cie, Libraries de l'Académie de Médecine, Paris, 1913.
1906: 3rd ICG, **London,** England. William Bateson/W. Wilks.
Report of the Third International Conference on Genetics, Royal Horticultural Society, London, 1906.
1902: 2nd ICG, **New York,** NY, USA. James Wood/Leonard Barron.
International Conference on Plant Breeding and Hybridization, Mem. Hort. Soc. NY, **Vol. 1**, 1903.
1899: 1st ICG, **London,** England. Sir J. J. Trevor Lawrence/W. Wilks.
International Conference on Hybridisation and Cross-Breeding of Varieties, J. Roy. Hort. Soc. **24,** 1900.

The first name indicated for each congress is that of the President; the second is that of the Secretary General, or equivalent, if recorded unambiguously in the proceedings. The bibliographic reference is that of the congress proceedings. Note that the first three ICGs were billed originally as conferences on plant breeding and hybridization; they were designated as "ICGs" at the 1906 meeting in London.

discussed at these congresses. It would be impossible to review them all in a short paper, but it would seem invidious to choose only a few. However, Jan and I share research interests in the molecular basis of genetic stability and change and the evolutionary relevance of these processes (Drake *et al.* 1998; Haynes 1987). Therefore, I decided to focus on early work concerning the nature of heritable variation that pointed the way toward current research on the mechanisms of mutagenesis and DNA repair.

In his plenary lecture at the 1963 ICG in The Hague, Demerec (1965) suggested that the first sixty years of genetical research was punctuated by a few distinct periods of exciting advances, each initiated by important discoveries or the introduction of new research methods. These were followed by a few years of humdrum activity devoted primarily to the detailed elaboration and implications of these advances. His choices for the six most influential developments were as follows: (1) "Rediscovery" of Mendel's papers and establishment



Left to right: Howard M. Temin, Jan Drake and his daughter Julie at the 16th International Congress of Genetics, Toronto, 1988.

of the generality of Mendel's laws for transmission of heritable traits; (2) introduction of Drosophila as a genetic system and elaboration of the chromosomal basis of heredity; (3) discovery that genetic changes can be induced by radiation; (4) discovery of the close correspondence between bands of Drosophila polytene chromosomes and positions of genetic loci in these chromosomes; (5) development of microbial systems for genetic analysis and discovery of the correspondence between genes and enzymes; and (6) discovery of the macromolecular structure of genetic material.

Obviously this list could be extended, especially if it was brought up to the year 1997. However, I doubt if these six items would be missing from anyone's register of the main events in genetics prior to 1963. I am surprised that he did not include as a seventh item the discovery of chemical mutagens which he and others discussed at the first two post-war ICGs in 1948 and 1953. Demerec presented his list just one year before the discovery in 1964 of nucleotide excision repair in DNA, an event that was to have a major impact on our present understanding of mutagenesis as a biochemical, as well as a physicochemical, process. The intimate relation between mutagenesis and genetically distinguishable modes of DNA repair was discussed for the first time at an ICG by Witkin (1969) and others in a symposium at the 1968 Congress in Tokyo.

A rough estimate of the relative levels of interest in the mechanisms of mutagenesis, as judged by successive ICG program committees, can be obtained from data on the number of plenary and symposium lectures devoted to this topic. Before the discovery of X-ray mutagenesis there was little to be said about the cause of mutations except that they were rare, sudden and discrete events that cause genes to pass from one stable state to another (Johannsen 1909).[4] The first paper on mutagenesis at an International Congress of Genetics was Muller's (1927) report on his X-ray work. At the next ICG in 1932, 20 percent of the main lectures were on this topic, the highest fraction ever. Approximately 10 percent of the invited presentations for the 12 subsequent congresses have been on some aspect of mutagenesis. Jumps above this historical average occurred at the 1948 ICG (to 13%) just after the first public report (in 1947) of chemical mutagenicity; next at the 1958 ICG (to 14%), the first to convene after the 1953 discovery of the structure of DNA; and then at the 1968 and 1973 ICGs (to 15% and 14%, respectively), increases related to the 1964 discoveries in the area of DNA repair. Since the 1983 congress there has been a steady decline to 5% in 1993. This relative decline reflects primarily the burgeoning interest in the application of genetic engineering techniques in medicine and agriculture.

Through the lens of my personal retrospectoscope, the historical path from views on heredity and variation in Darwin's day to contemporary studies on DNA repair and mutagenesis looks more like a strange kind of slalom course than a smooth escalator to the stars. Many troublesome slalom gates of received wisdom had to be avoided along the course of discovery, but as each gate was bypassed new ones jumped up in surprising places along the way. Of course this phenomenon is not unique to genetics. Scientists, like most other people, abhor a conceptual vacuum. Whenever one appears it is as often filled with personal prejudices as with new, testable ideas. It is unfortunate that past misconceptions are often forgotten by working scientists. The tendency to disregard the ragged course of history makes it difficult

[4] The earliest discussion of the nature and possible causes of heritable variations that I have found is that given by the 17th century English physician and writer, Sir Thomas Browne, author of *Religio Medici*. In his *Pseudodoxia Epidemica*, one of the first influential attacks on vulgar superstition in England, he wrote, regarding patterns of heritable coloration in animals and humans: ". . . we may say that some Chaughes came to have red legs and bils, that some Crowes became pyed; all of which mutations however they began, depend on durable foundations, and such as may continue forever. And if as yet we cannot satisfie, but must farther define the cause and manner of this mutation; we must confesse in matters of Antiquity, and such as are decided by History, if their Originals and first beginnings escape a due relation, they fall into great obscurities, and such as future Ages seldome reduce unto a resolution" (Browne 1646, p. 328). At the end of the chapter in which he discusses these questions he even anticipates the idea of a "separation" of genetic elements in the formation of sperm!

for graduate students to appreciate how *we* got where we are, and why *they* are doing what they are doing, apart from getting the Ph.D. union card. It is for these reasons that I offer my list of some of the more significant gates which were finessed *en route* to our present understanding of the mechanisms which promote gene stability but allow genetic change: (1) Discontinuous variations are not important for evolution; (2) discontinuous "Mendelizing" variations may be regarded as "unit-characters," an intimate one-to-one association of heritable "units" and the "characters" they control; (3) the genetic units themselves are hypothetical entities, immaterial "powers or faculties" not necessarily associated with chromosomes; (4) mutations are "explosive" events of some kind or spontaneous "quantum jumps," probably noninducible in the laboratory by physical or chemical agents; (5) genes are unusually stable aggregations of atoms or molecules, perhaps even a special state of matter obeying "other laws of physics" unique to living organisms; (6) genes are made of protein, or are "nucleoprotein particles" in which the genetic specificity resides only in the protein component; (7) unlike RNA and protein, DNA is not subject to metabolic "turnover" in cells, presumably what one would expect of genetic material; and (8) under normal physiological conditions, the intracellular environment provides an innocuous, hazard-free home for the genetic material.

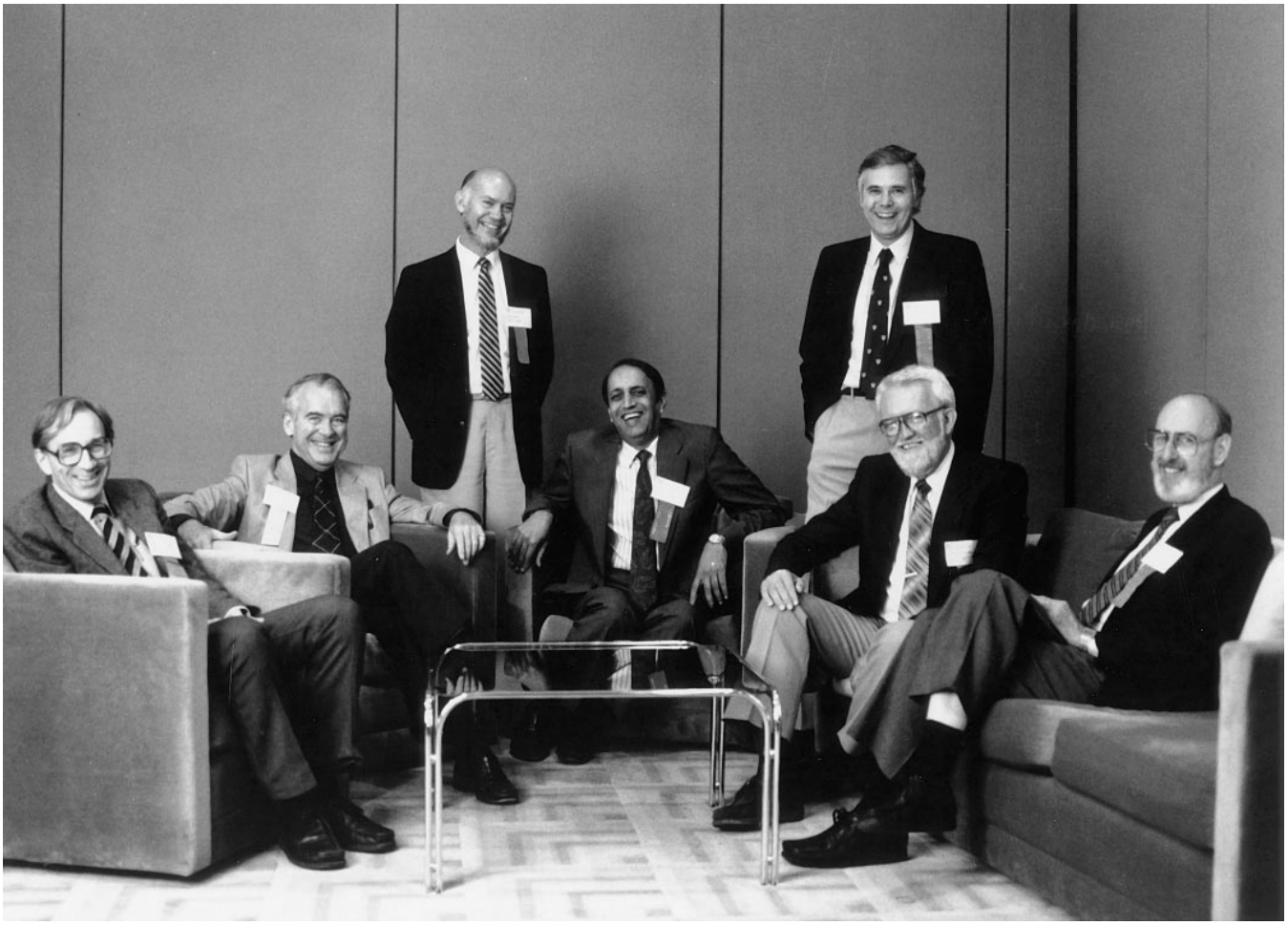
This list also could be extended, but these items reveal how much the catechism of heredity and variation has changed from the days of Darwin (1868) to those of Drake (1989, 1991; Drake *et al.* 1983; see also Friedberg *et al.* 1995 and Tibs 1995). In no sense do I mean to belittle the contributions of those whose names are associated with any of the above-mentioned ideas. As science advances, the doctrines and received wisdom of today always have a good chance of being seen as mistakes tomorrow. In this article I outline some of the historical developments associated with the first three items on Demerec's list in the context of the first five misconceptions on my list. I have discussed the remaining items on my list elsewhere (Haynes 1985). In this article I emphasize the work and activities of William Bateson because I consider him to be the main founding father of 20th century genetics as a branch of biology. Furthermore, the formal establishment of genetics was initiated by him, largely within the context of the first three "International Congresses of Genetics."

Darwin's infinitesimal variations: Darwin was acutely aware that nothing was known in his day about the mechanisms of heredity and variation, the phenomena upon which his mechanism of natural selection must depend if it was to exist. As some wag once wisely said, "selection can explain the survival but not the arrival of species." Even in the first edition of the *Origin* Darwin stated, immediately following his definition of natural selection, that ". . . unless profitable variations do occur, natural selection can do nothing" (Darwin 1859, p. 82). He devoted chapter 5 of the *Origin* to the "Laws of Variation" in which he confessed that "Our ignorance of the laws of variation is profound" (p. 167), and he concluded this rather unsatisfactory chapter as follows (p. 170): "Whatever the cause may be of each slight difference in the offspring from their parents—and a cause for each must exist—it is the steady accumulation, through natural selection, of such differences, when beneficial to the individual, that gives rise to all the more important modifications of structure, by which the innumerable beings on the face of this earth are enabled to struggle with each other, and the best adapted to survive." All that he could offer by way of a physiological mechanism (p. 131) was the following: "Some authors believe it to be as much the function of the reproductive system to produce individual differences, or very slight deviations of structure, as to make the child like its parents. . . . The reproductive system is eminently susceptible to changes in the conditions of life; and to this system being functionally disturbed in the parents, I chiefly attribute the varying or plastic condition of the offspring."

Darwin's innumerable, microscopic "individual differences" generated according to unknown laws of variation among offspring by parental reproductive systems are metaphorically equivalent to the "background noise" in telecommunication and other electronic systems. Thus natural selection may be viewed as acting like a (Maxwellian-style) "Darwinian Demon" capable of seizing imperceptible fluctuations which happen to occur in an adaptive direction relative to the environment, and then accumulating them in this direction over many generations, or until a countervailing change in the environment occurs. As I understand it, this is the essence of Darwin's picture of the "mutability of species."[5] To the dismay of Thomas Henry Huxley, Darwin largely rejected "discontinuous variations" as significant factors in evolution[6]—*natura non facit saltum!*

[5]Darwin originally used the word "transmutation" (with no alchemical reference intended) in the context of species change over time (Darwin 1888, pp. 82 and 276). Later, William L. Tower discussed the ways in which "sudden transmutation in the germinal material" might be produced by "forces external to the organism" (including radium emanations), as well as by hybridization and selection. His 125 page chapter provides an interesting popular overview of attempts to induce mutations artificially prior to Muller's discovery of X-ray induced mutations in Drosophila (Castle *et al.* 1912). Soddy and Rutherford also used the term "transmutation" (with alchemical resonance intended) in connection with their discovery of the artificial transformation of atomic nuclei. The use of this word by scientists unfortunately conjures in the minds of many people fearful images of alchemists or mad scientists tinkering with the sacrosanct mysteries of nature (Haynes 1994; Weart 1988).

[6]Darwin insisted that his infinitesimal "individual variations" were almost certainly the sole cause of evolution *in the wild.* However, he did cite instances where he believed that the appearance of new varieties *under domestication* (*e.g.*, in pigeons and many plants) probably arose from "sports" or "bud variation" produced "spontaneously" by unknown causes (Darwin 1868, Vol. 1, chaps. 6 and 11).



Executive Committee, 16th International Congress of Genetics, Toronto, 1988. *Standing, left to right:* K. J. Kasha (Canadian Program Committee), J. W. Drake (International Program Advisory Committee). *Seated, left to right:* J. D. Friesen (Local Arrangements Committee), R. H. Haynes (President), A. Nasim (International Coordinator), D. B. Walden (Secretary General), J. A. Heddle (Local Arrangements Committee). *Absent from photo:* R. B. Church (Finance Committee), L. Forget (Congress Manager), D. Ruest (Assistant Congress Manager), L. Siminovitch (Honorary President).

In the third scientific book that he wrote after the *Origin*, Darwin published his provisional hypothesis of pangenesis. This was a fanciful "atomistic" theory of inheritance which explained both the generation of variant offspring under changing conditions of life and the effects of "use and disuse" in producing evolutionarily relevant variations (Darwin 1868).

Bateson's discontinuous variations: Genetics must be one of the few major fields of biology whose establishment is normally dated by historians to a specific year—1900—even though its antecedents in systematic work on plant hybridization date back at least to the observations of Joseph Kölreuter published first in 1761 (Roberts 1929; Olby 1966). The curious story of the resurrection of Mendel's 1866 paper, and its citation (as opposed to suppression) in the 1900 papers on plant hybridization by Hugo De Vries, Carl Correns and Erich Von Tschermak-Seysenegg, has been exhaustively analyzed for evidence of priority game-playing among the principals involved (Sturtevant 1965; Carlson 1966; Hartl and Orel 1992; Orel 1996).[7] However, it was the energetic enthusiast William Bateson, never one to shrink from controversy, who was to become as much "Mendel's Bulldog" as T. H. Huxley was "Darwin's Bulldog" some 40 years earlier.

It was Bateson, I think even more than De Vries (1901–1903),[8] who undermined the 19th century focus

[7] Stern and Sherwood (1966) have assembled a valuable compendium of English translations of the foundation papers of Mendelian genetics.

[8] I consider De Vries' small book on his theory of *intracellular* pangenesis to be much more interesting today than his large treatise on the mutation theory. In the former, he proposes that inheritance is controlled by innumerable molecular aggregates similar to Darwin's "gemmules." However, De Vries' pangenes are not transported through the body (with the reproductive cells serving as a kind of reservoir) but rather are localized *within* cells. Division of the nuclei takes place in such a way that the many kinds of pangenes are distributed evenly over the two daughter cells. All the pangenes from which an organism develops remain represented in the nuclei of every cell, *i.e.*, nuclei are genetically totipotent. More specifically, following a

of Darwin's followers on the role of infinitesimal, and generally imperceptible, "continuous variations" in evolution. In this he pointed the way to new approaches for research on the inheritance of readily observed "discontinuous variations." When the dust had settled after his bitter personal war with his mentor and onetime closest friend W. F. R. Weldon he had, nonetheless, established "atomistic" Mendelian theory as the most promising road ahead for research on heredity and variation (Provine 1971). However, the old Darwinians were by no means converted to the new approach *en masse*. Three years before his death in 1913 at age 90, Alfred Russel Wallace, the codiscoverer of natural selection, wrote that "The facts outlined . . . furnish a sufficient reply to those ill-informed writers who still keep up the parrot-cry that the Darwinian theory is insufficient to explain the formation of new species by survival of the fittest. . . . They also serve to rule out of court, as hopelessly inefficient, the modern theories of 'mutation' and 'Mendelism,' which depend upon such comparatively rare phenomena as 'sports' and abnormalities, and are, therefore, ludicrously inadequate as substitutes for the Darwinian factors in the world-wide and ever acting processes of the preservation and adaptation of all living things. . . . The persistency of Mendelian characters is the very opposite of what is needed amid the ever-changing conditions of nature" (Wallace 1911).

Bateson recognized that natural selection was a *necessary* condition for evolution but did not believe that it was also a *sufficient* explanation, primarily because so little was known about the facts of heritable variation. I doubt that Darwin would have disagreed with this assessment.

In 1894 Bateson published his monumental 598 page treatise *Materials for the Study of Variation, treated with especial regard to Discontinuity in the Origin of Species*. In the preface he wrote "Whatever be our views of Descent, Variation is the common basis of all of them. . . . Difficulty has hitherto arisen from the fact that Variation is not studied for its own sake." In the introduction (p. 6) he states his conviction that ". . . the different forms of life are related to each other, and their diversity is due to Variation. On this hypothesis, therefore, Variation, whatever may be its cause, and however it may be limited, is the essential phenomenon of Evolution. Variation, in fact, *is* Evolution. The readiest way, then, of solving the problem of Evolution is to study the facts of Variation." Bateson's *Materials* bears a curious resemblance to Darwin's *Origin*. In it he assembled an extraordinarily large and taxonomically diverse collection of detailed facts about variation and inferred from them his general (but rather metaphysical) conclusion that ". . . *the Discontinuity of Species results from the Discontinuity of Variation*" (his emphasis). In later years it became evident that not all the examples of variation cataloged by Bateson were heritable. Like others at the time, Bateson tended to assume that there was a one-to-one relationship between unitary genetic factors and their associated heritable traits (the "unit-character" conflation).

Bateson reiterated his 1894 call for a new research emphasis on the study of discontinuous variations on the first day of the 1899 conference on hybridization of the Royal Horticultural Society (RHS) held at Chiswick in London. It was the lead paper in the proceedings of this first international conference on this subject (Bateson 1900a).[9] In 1906 this meeting was designated as the "1st International Conference on Genetics" (Table 1 and Bateson 1906).[10]

Less than a year later (May 8 1900), while on a train to London to speak again to the RHS, Bateson read Mendel's paper on Pisum for the first time. His wife Beatrice commented in her memoir of his life, "As a lecturer he was always cautious, suggesting rather than affirming his own convictions. So ready was he however for the simple Mendelian law that he at once incorporated it into his lecture" (Bateson 1928).

In light of his subsequent fervor in promoting Mendelism, I think it is fair to say that Bateson experienced a veritable *Illuminationem* on the train to London that day. At the meeting he gave a clear and succinct summary of Mendel's paper. He introduced it in the following prophetic way: "These experiments of Mendel's were carried out on a large scale, his account of them

suggestion by Roux, he recommends that the pangenes should be looked for in the chromosomes. Except for those pangenes that dominate nuclear division, all others must migrate from the nucleus to the cytoplasm in order to become active in specific tissue differentiation. Thus, the cytoplasm of any given cell contains only those pangenes that are active in it. Classes of pangenes can differ both quantitatively and qualitatively. Quantitative variations in pangenes give rise to Darwin's fluctuating or individual variations. Qualitative changes in pangenes give rise to "species-forming" variability. These changes come about because the pangenes replicate to produce two new pangenes that are like the original one, but that exceptionally these two new pangenes may be dissimilar. The foregoing summary is essentially a *précis* of the author's own words (De Vries 1889, pp. 213–216).

[9] The President of this conference, Sir J. J. Trevor Lawrence, was the only "geneticist" to be depicted in a *Vanity Fair* cartoon ("Men of the Day." No. 736. January 26, 1899; "Spy" was the cartoonist). He was 67 at the time and was described in the note accompanying the cartoon as follows: "Born in London, he is naturally a gardener; so that he has been President of the Royal Horticultural Society (for which he has done so much) for nearly 20 years. . . . He is a Wykehamist who became a medical student at St. Bartholomew's, joined the Indian Medical Service, and went through the Mutiny. Then he took to gardening, and some years later went into Parliament: where he wasted about seventeen years of his life. Since then he has given himself up to recreation; his hobbies being the breeding of orchids and the collecting of objects of Japanese art. . . . He is an agreeable fellow of simple tastes and much energy." I arranged for a color copy of the original print to be reproduced on the back cover of the Registration Bulletin for the 1988 International Congress of Genetics in Toronto.

[10] The word "Congress" was first used for the 1927 meeting in Berlin. The four previous meetings were called "Conferences." However, in his Presidential Address at the third meeting, Bateson did refer to it as a Congress (Bateson 1906).

is excellent and complete, and the principles which he was able to deduce from them will certainly play a conspicuous part in all future discussions of evolutionary problems" (Bateson 1900b). He also asserted that "this is preeminently a subject in which we must distinguish what we *can* do from what we want to do. We *want* to know the whole truth of the matter; we want to know the physical basis, the inward and essential nature, the 'causes' . . . of heredity. We want also to know the laws which the outward and visible phenomena obey" (Bateson's emphasis). In the second part of his paper, printed in the same volume, he declared that Mendel's "experiments are worthy to rank with those which laid the foundations of the Atomic laws of Chemistry" (Bateson 1900c).

In his book *Mendel's Principles of Heredity*, he concluded his historical introduction by claiming that "Had Mendel's work come into the hands of Darwin, it is not too much to say that the history of the development of evolutionary philosophy would have been very different from that which we have witnessed" (Bateson 1902a). He also reprinted his English translation of Mendel's paper on Pisum[11] together with a translation of Mendel's paper on Hieracium, and concluded the book with a lengthy rebuttal, intemperate by today's polite standards of scientific debate, of Weldon's (1902) sharp, but not unreasonable, criticisms of Mendel's work and interpretations. The book appeared shortly before he attended the 1902 meeting on hybridization in New York, also designated in 1906 as the "2nd International Conference on Genetics."

In New York Bateson once again took the opportunity to spread the gospel according to Mendel, but with special emphasis on the relevance of the segregation of "antagonistic allelomorphic characters" to the "hopeless entanglement of contradictory results" of plant hybridizations. He asserted that "We have for the first time a conception of the true nature of at least a part of the facts which underlie the outward and visible phenomena witnessed by the breeder" (Bateson 1902b). It is difficult today to appreciate how irritating, and inexplicable, the frequent intergenerational disappearances and reappearances of visible traits must then have been to breeders, farmers and horticulturalists. On the basis of the published discussion of his paper, it is clear that he was well-received and convinced the many plant breeders in his audience of the revolutionary importance of Mendel's ideas for their hybridization programs. On October 3, the day after the close of the conference, he wrote to his wife as follows: "My own performances are over, and I believe passed off well . . . At the train yesterday, many of the party arrived with their *Mendel's Principles* in their hands! It has been "Mendel, Mendel all the way," and I think a boom is beginning at last. . . . I am glad to be right in the swim" (Bateson 1928).

Bateson coined the word "genetics" in 1905 to describe the new scientific enterprise that he was striving mightily to establish as a formal academic discipline. In a letter to Professor Adam Sedgwick regarding his candidacy for a new Professorship at Cambridge, which he hoped would be in his area of interest, he commented that as a descriptor for his field no single word in common use carries the combined meaning of heredity with the "cognate" phenomena of variation: "Such a word is badly wanted, and if it were desirable to coin one, 'GENETICS' might do" (Bateson 1928, p. 93).[12]

In 1906 he served as President of another International Conference on Hybridization and Plant Breeding organized by the RHS in London. At his suggestion it was agreed to rename it as the "3rd International Conference on Genetics" with the two preceding hybridization conferences designated retrospectively as ICGs. He spoke to this point as follows: ". . . the science itself is still nameless, and we can only describe our pursuit by cumbrous and often misleading periphrases. To meet this difficulty I suggest for the consideration of this Congress the term Genetics, which sufficiently indicates that our labours are devoted to the elucidation of the phenomena of heredity and variation: in other words, to the physiology of Descent, with implied bearing on the theoretical problems of the evolutionist and the systematist, and the application to the practical problems of breeders, whether of animals or plants. After more or less undirected wanderings we have thus a definite aim in view." I think of the first three horticulturally oriented ICGs as the "Batesonian Congresses." Genetics thus became established as a new branch of biology, with a new name, rooted initially in the botanical tradition of plant hybridization.

Bateson was appointed Professor of Biology at Cambridge in 1908. The position was funded for five years by an anonymous donor to mark the centenary of Darwin's birth and the jubilee of the publication of the *Origin of Species*. It was stipulated that the holder of the chair was to devote himself to "those subjects which were the chief concern of Darwin's life work . . . in that branch of Biology now entitled Genetics" (Bateson 1928). In his inaugural lecture as Professor he reveals (to the reader today) how badly off course he was in his conception of the purely functional, immaterial nature of hereditary determinants as the "power or faculty to produce the ferment or the objective substance." Still, his passion for genetics shines through (Bateson 1908). Two years later he became the first Director of the new John Innes Horticultural Institute at Merton Park in south-west London.

[11] First published in 1901 (J. Roy. Hort. Soc. **26:** 1–32).

[12] Bateson did not get the professorship; it was awarded instead to Sedgwick in parasitology.

In retrospect, Bateson's new field was hobbled at birth by his notion of "unit-characters," a phrase which, in later parlance, obscures the important distinction between genotype and phenotype. His initial denial of the material nature of the segregating units, and his "presence-absence" hypothesis to explain the distinction between dominant and recessive unit-characters were equally unfortunate (Allen 1978; Carlson 1966). However, his rather uncritical definition of unit-characters was sufficient for his immediate purposes, and this idea at least enabled him *to do* what someone with no significant knowledge of cytology or chemistry *could do* at the time. Unfortunately these deficiencies, and his understandably high regard for his own approach to research, made it difficult for him to accept for many years the "chromosome theory" of inheritance elaborated by Thomas Hunt Morgan and his collaborators at Columbia University. It was not until 1922, after a visit of some weeks at Morgan's home and lab, that he became convinced of the merit of the chromosome theory (Allen 1978). In a setting strangely reminiscent of his Mendelian illumination on the train to London in 1900, he travelled from New York to Toronto to attend the annual meeting of the American Association for the Advancement of Science. There, in his Vice Presidential Address, he announced that he could no longer maintain his ". . . skepticism as to the direct association of particular chromosomes with particular features of the zygote. The transferrable characters borne by the gametes have been successfully referred to the visible details of nuclear configuration" (Bateson 1922).

Unlike his fulsome conversion to Mendelism, his acceptance of the chromosome theory was neither complete nor enthusiastic. In a long paper published in 1926, the year of his death, he wrote: " . . . we shall do genetical science no disservice if we postpone acceptance of the chromosome theory in its many extensions and implications. . . . with ever increasing certainty, the conviction has grown that the problem of heredity and variation is intimately connected with that of somatic differentiation . . . the chromosome theory, though providing much that is certainly true and of immense value, has fallen short of the essential discovery" (Bateson 1926a). In contrast with this statement, it is interesting to note that also in 1926 three articles by him appeared in the 13th edition of the *Encyclopædia Britannica* (on Genetics, Mendelism and Sex). In the article on Mendelism, he describes Johannsen's distinction between genotype and phenotype but makes no mention of unit-characters. However, he maintains a slightly modified version of his presence-absence hypothesis, called here "addition and loss," to explain the distinction between dominant and recessive variations. In the Genetics article, he includes cytology and embryology along with breeding as the three most important experimental approaches for research in genetics; he points out that genetic "units," or determining factors, may be called "genes"; he recognizes the plausibility of the chromosome theory, and finally applauds Morgan's discovery of linkage (formerly he had called this "gametic coupling"). "The first development of this conception was made by T. H. Morgan, whose investigations relating mainly to the fruit-fly Drosophila, have inaugurated a new phase in the development of genetical theory" (Bateson 1926b).

Morgan's chromosomes: In the early part of his career Morgan was sceptical about Darwinism, Mendelism *and* the cytologists' chromosomal theory of inheritance (for a thorough review of the latter see Wilson 1896). However, the interplay of his interests in evolution, in Wilhelm Roux's *experimental* approach to embryology (*Entwichlungsmechanik*) and in De Vries' mutation theory led him to begin work (around 1908) with Drosophila. He sought first to induce De Vriesian macromutations by exposing the flies to various chemical insults and radium emanations (Allen 1978). After a year of failure in this effort, he happened to notice in his stocks a fly with white eyes rather than the usual red eyes. Breeding experiments revealed that the white-eyed mutation was inherited in a Mendelian fashion and was sex-linked. In my view this chance discovery marks the beginning of the "golden era" of classical genetics which Crow (1992) sees as nearing its end around the time of the 6th International Congress of Genetics, of which Morgan was President, held at Cornell University in 1932.

A few years later Morgan and his students published a highly influential textbook of genetics (Morgan *et al.* 1915). The final chapter on the "Factorial Hypothesis" contains a discussion of several serious misconceptions introduced into the field by the unit-character idea and Bateson's presence-absence hypothesis: "As soon as the individuals differ by two or more genetic factors that affect the same character the latter can no longer be considered a unit. So much misunderstanding has arisen among geneticists themselves through the careless use of the term unit character that the term deserves the disrepute into which it is falling" (p. 210). It is interesting to note that the word "factor" is used throughout this book, rather than Wilhelm Johannsen's (1909) term "gene." It would appear that this usage was quite deliberate. It was based on the authors' desire to distance their belief in a distinct material basis for heredity from Johannsen's "mathematical" concept of the gene "fully free from every hypothesis" as to its nature (Allen 1978). However, within two years Morgan was no longer hesitant about this terminological nicety and the material gene came into mental view (Morgan 1917, 1919).

Once geneticists became convinced that the unit component of Bateson's unit-characters, and Morgan's genetic factors, were material entities or genes located at specific positions along chromosomes, one might have expected that the chemistry of the genetic substance,

and the mechanism of mutation, would soon become known. The problem had been posed quite explicitly by Morgan's close friend (and former colleague at Bryn Mawr College) Jacques Loeb. It is a tribute to Morgan's character that he was a close friend simultaneously with the arch-mechanist Loeb and the arch-vitalist Hans Driesch (Allen 1978). In 1911 Loeb argued, in connection with recent discoveries regarding fertilization and the chromosomal basis of sex determination, "The main task which is left here for science to accomplish is the determination of the chemical substances in the chromosomes which are responsible for the hereditary transmission of a quality, and the determination of the mechanism by which these substances give rise to the hereditary character. . . . We may, therefore, say that the solution of the riddle of heredity has succeeded to the extent that all further development will take place purely in cytological and physico-chemical terms" (Loeb 1912). Forty years were to pass before Loeb's physico-chemical task could be tackled with any real prospect of success, even though many important cytogenetic and microbiological discoveries were made during this period. Classical genetics provided the phenomenological basis for the advent of molecular biology in the mid-fifties (McElroy and Glass 1957; Anfinsen 1959; Strauss 1960). The complementary relation between classical and molecular approaches to genetics was nicely captured recently in a remark by a Russian colleague: "If one views molecular biology as a tool, such as a spade, then it is the study of phenomenology that shows where to dig" (Korogodin 1993).

Morgan reviewed the then current situation in basic genetics in his Silliman Memorial Lectures at Yale University. He drew particular attention to the problem of *gene stability*. He commented that ". . . it has been implied that the gene is a stable element in heredity, but whether it is stable in the sense that a chemical molecule is stable, or whether it is stable only because it fluctuates quantitatively about a persistent standard, is a question of theoretical and perhaps of fundamental importance. . . . Since the gene cannot be studied directly by physical or chemical methods, our conclusions concerning its stability must rest on deductions from its effects." In his concluding remarks he stated: "The only practical interest that a discussion of the question as to whether genes are organic molecules might have would relate to the nature of their stability. . . . If the gene is regarded as merely a quantity of so much material, we can give no satisfactory answer as to why it remains so constant through all the vicissitudes of outcrossing, unless we appeal to mysterious powers of organization outside the genes that keep them constant" (Morgan 1926).

At the 1927 International Congress of Genetics held in Berlin, it was decided to hold the next congress in the United States five years hence. Morgan had little interest in attending large international meetings (G. E. Allen, personal communication). However, in 1929 he was unanimously elected President of the 6th International Congress of Genetics to be held at Cornell University in 1932 (for a more detailed description of this Congress see Crow 1992).

In closing his Presidential Address Morgan listed what he considered to be the five most important problems for geneticists in the immediate future. He described one of these as follows: "The nature of the mutation process—perhaps I may say the chemico-physical changes involved when a gene changes to a new one. Emergent evolution, if you like, but as a scientific problem, not one of metaphysics." In his final paragraph on how these discoveries might be made he slyly—and I think wisely—said that these advances would be achieved most efficiently by "not holding genetics congresses too often" (Morgan 1932).

Muller's mutations: Muller gave the first full report on his discovery of X-ray induced mutations in Drosophila at the 5th International Congress of Genetics in 1927 in Berlin (Muller 1928). His last-minute frenzy in preparing his text, and the instant celebrity he met upon his return home, has been graphically described by Stern (1974), Carlson (1981) and most recently by Crow and Abrahamson (1997) who rightly say that Muller's paper "opened a new era in genetics." Before leaving for Berlin, he published a brief paper in Science to establish priority for his discovery of X-ray mutagenesis. It appeared with the sensational title *Artificial transmutation of the gene*, but with no biological data or radiation doses—merely qualitative observations and some discussion: "Thus we may hope that the problems of the composition of the gene can shortly be approached from various new angles, . . . so that it will be legitimate to speak of the subject of 'gene physiology,' at least, if not gene physics and chemistry" (Muller 1927).

This was a great phenomenological discovery. However, neither Muller's X-ray results, nor those of the many radiation geneticists who followed him, opened the door to the identification of the chemical nature of the gene, or to the molecular mechanisms of mutagenesis. Its most important impact on genetics turned out to be practical rather than theoretical. He recognized this in his 1927 paper: ". . . it should be possible to produce, 'to order,' enough mutations to furnish respectable genetic maps . . . and, by the use of the mapped genes, to analyze the aberrant chromosome phenomena simultaneously obtained . . ." Furthermore the discovery sensitized him immediately to the health hazards of the careless or excessive use of diagnostic X-rays in medical practice, and later of radioactive fallout from nuclear weapons tests (Muller 1927; Carlson 1981).

Despite the excitement generated by Muller's report of his discovery of X-ray mutagenesis in Berlin, five years later only three of the approximately 200 short papers presented at the 1932 ICG at Cornell were on mutagenesis. However, of the 18 plenary addresses, three were on mutagenesis (by H. J. Muller, L. J. Stad-

ler and N. W. Timoféeff-Ressovsky, respectively). Carlson (1981, pp. 181–183) records a troubling description of Muller's agitated behavior while presenting his paper as recalled later by his former student Bentley Glass.

At the 1939 International Congress of Genetics (Edinburgh), three papers containing measurements of the UV action spectra for induced mutagenesis implicated DNA as the primary molecular target for the effect of 254 nm UV. In one of these Stadler (1941) reported his comparative studies of monochromatic UV and X-ray induced mutagenesis in maize pollen. He concluded also that the dependence of mutation on chromosome rearrangement had been over-emphasized and that there is "no evidence of any genetic distinction between (mutations) produced by ultra-violet and those produced by X-rays." All three independent sets of UV action spectroscopy data for UV-induced mutagenesis were found to resemble the UV absorption spectrum for DNA (Stadler 1997). However, this did not convince biochemists that DNA, then thought to consist of repetitive, covalently linked tetranucleotide groups, was the genetic material (Levene 1921). Many years later, Alexander Hollaender, one of those who also presented such data at this meeting, told me that these findings stimulated his life-long interest in research on nucleic acids. However, Muller was not convinced by these results, and Hollaender also told me that it was for this reason that he did not press a genic interpretation for them.

Timoféeff's targets and Delbrück's genes: In his contribution to the Edinburgh congress, Timoféeff-Ressovsky (1941) reviewed his extensive work on X-ray mutagenesis in Drosophila and his pioneering interpretation of mutagenicity data in terms of the classical target theory (Timoféeff-Ressovsky and Zimmer 1947; Zimmer 1961). The application of target theory to problems in cellular radiobiology was adopted by some of the physicists who, during the second world war, chose to begin their research careers in medical physics or radiation biology because they could not, in good conscience, work on weapons development, particularly nuclear weapons (*e.g.*, Lea 1946).[13] Timoféeff also discussed spontaneous mutagenesis on the basis of Max Delbrück's "quantum mechanical model" of the gene (Timoféeff-Ressovsky *et al.* 1935). In later years Delbrück sometimes referred to this paper as "a silly piece of work." However, it did have a surprising impact on the development of molecular biology.

As a result of reading Schrödinger's (1944) popular account of "Delbrück's model," a number of young physicists saw that the physical basis of gene stability, together with the nature of the initial physical processes of mutation induction by ionizing radiation, offered intellectually challenging problems that might lead to the discovery of "other laws of physics" (Zimmer 1966; Fischer and Lipson 1988; Haynes 1993). The philosophical background to Delbrück's interest in these matters, which was derived from Bohr's ideas on complementarity in quantum mechanics, was elegantly reviewed by Gunther Stent (1989), Max's first post-doctoral fellow, in the Delbrück Lecture at the 16th International Congress of Genetics in Toronto.[14]

Like Morgan (1926) before him, Delbrück realized that the molecular basis of gene stability must be solved before the mechanism of gene mutation could be approached with any prospect of success. It was on account of his long-time interest in the problem of gene stability that Max was invited to lead the final discussion at the first symposium on DNA repair (Haynes *et al.* 1966). Genetic change cannot be understood as long as the structures and processes responsible for genetic stability remain unknown.

An analogous situation once existed in the realm of atomic physics. The stability of the original Rutherford atom model was inconsistent with classical electrodynamics: negatively charged electrons in circular orbits around a positively charged nucleus would radiate energy and spiral into the nucleus. Thus Rutherford's first atom model was not a stable structure. This problem was resolved through the development of quantum mechanics, and with this there emerged, *ipso facto*, the basis for our present insight into the mechanisms of atomic and molecular change.

Once it became established that certain chemicals could produce mutations, the gene lost its mysterious

[13] For example, my post-doctoral supervisor in the Physics Department at St. Bartholomew's Hospital Medical College in London, the nuclear physicist Joseph Rotblat, resigned his job on the atomic bomb project at Los Alamos when it became clear to him that Germany would be unable to build such a device. He returned to England where he took up research in medical physics and radiation biology. On July 9, 1955, at Caxton Hall in London, Bertrand Russell launched the Russell-Einstein Manifesto, for the abolition of nuclear weapons and the peaceful settlement of international disputes. Russell asked Rotblat to be chairman of the meeting. Einstein had signed the Manifesto just before his death a few months earlier. It was signed also by six other Nobel Laureates. The only biomedical scientist who was invited to sign was Muller on account of his expertise on, and concern over, the genetic effects of radiation. After the Caxton Hall meeting, Russell and Rotblat arranged for a meeting of 21 distinguished scientists (mostly physicists plus one lawyer) to discuss the consequences of the use of nuclear weapons, their control and the responsibilities of scientists. At the invitation of the industrialist Cyrus Eaton, the meeting was held at his summer home in Pugwash, Nova Scotia. This led to the establishment of the continuing "Pugwash Conferences on Science and World Affairs" with Rotblat at the helm. In 1995, Rotblat received the Nobel Prize for Peace (shared with the Pugwash organization itself).

[14] Delbrück never presented his theory of gene stability at an ICG. However, he did give a paper describing his work with bacteriophages at the 8th congress in 1948 at Stockholm (Delbrück 1949). It is interesting to note that his 1935 paper with Timoféeff-Ressovsky and Zimmer was for a time referred to, rather perjoratively, as the *Dreimännerwerk*, not for any scientific reasons, but because it was then highly unusual for three scientists from different fields to undertake collaborative research in Germany (Zimmer 1966).

status as a special state of matter obeying "biotic" laws of physics complementary to those observed in inanimate matter. At the 1948 International Congress of Genetics held in Stockholm, Auerbach (1949) reviewed her recently declassified discovery of the mutagenicity of the "radiomimetic" alkylating agent known as mustard gas; Demerec (1949) and Koller (1949) also gave papers on chemical mutagenesis. These results suggested that genes were composed of "ordinary" molecules which were widely thought to be nucleoproteins. As a result of the discovery of chemical mutagenesis Muller, writing in 1952, prophetically suggested that mutations arise from "a biochemical disorganization in which the processes normally tending to hold the mutation frequency in check are to some extent interfered with" (Muller 1954).

Muller's speculations on the role of metabolism in mutagenesis have been born out in many ways. First, there exist mechanisms which promote the accuracy of genetic information transfer and effect the repair of DNA damaged by normal metabolites, as well as by xenobiotic chemicals (Kirkwood *et al.* 1986). Second, there evidently exist significant relations, that so far have not been sorted out at the genetic and molecular levels, among the various manifestations of nucleic acid metabolism as seen in DNA replication, repair, recombination and most recently in transcription-coupled repair (Hanawalt 1994; Tournaletti *et al.* 1997). These mechanisms are highly conserved phylogenetically. In addition, the genetic effects induced by radiations and chemical mutagens also can arise from disturbances in deoxyribonucleotide (dNTP) pools and metabolic pathways in cells and organisms. Such disturbances can be produced genetically or by exposure to drugs, such as the antifolates, which inhibit certain enzymes involved in dNTP biosynthesis (MacPhee *et al.* 1988; Kunz *et al.* 1994; McIntosh and Haynes 1997). With these discoveries, the analysis of genetic stability and change has transcended the scope of simple physicochemical theory. To further enrich our understanding of the mechanisms of mutagenesis we must enter the complex realm of cellular homeostasis and metabolic circuit analysis. Biochemists may well ask "What's an old *physicist-manqué* like you doing in a field like this?"

À bientôt à Beijing: Only one geneticist from China attended the 1948 International Congress of Genetics, the first to be held after the end of the second world war. His name was C. C. Tan (or Tan Jiazhen in the contemporary transliteration of his name). He was already an internationally-known Drosophila geneticist and professor of biology at the National Chekiang University in Hangchow. However, at Stockholm he gave a paper on a line of work that he had pioneered (1930–1933) in China as a Master's degree student with Prof. J. C. Li of Yenching University, Beijing. It concerned further studies on the seasonal variations of color patterns in the Asiatic lady-bird beetle, *Harmonia axyridis* (Tan 1949). He received his Ph.D. in 1937 under the supervision of Theodosius Dobzhansky at Caltech. T. H. Morgan and A. H. Sturtevant also were his teachers. Over the course of his long career he has had the good fortune of meeting, and in many cases working with, some of the most prominent leaders in genetics. The many photographs published together with a collection of his scientific papers testify to the fact that he is an extraordinary link with the past, a link that remains strong and vital (Tan 1992).

During the second Plenary Session of the Stockholm Congress, Tan was elected as a member of the Permanent International Committee which had been established in 1932 at the 6th ICG to oversee the organization of future congresses. I happen to know that to be President of the first International Congress of Genetics to be held in China marks the fulfilment of a hope and ambition that has been with him throughout his many years of faithful service to genetics. He has met with much success in his research and in building genetics at Fudan University in Shanghai; but also with much torment and despair during the dark days of the infiltration of Lysenkoism into China (Tan 1989).

International Congresses of Genetics provide a special opportunity, one that comes but once every five years, for geneticists to view the full sweep of their ever-changing field, and to cement friendships among colleagues from all parts of the world. This certainly will be the case for those of us who live in the Americas or Europe and attend the next ICG in Beijing. It will be an historic event for which Jan Drake and C. C. Tan have worked long and hard.

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