Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

SEWALL WRIGHT AND PHYSIOLOGICAL GENETICS

SEWALL WRIGHT celebrated his 97th birthday anniversary on December 21, 1986. He is the last survivor of the pioneers who founded twentieth-century genetics. His first genetical paper was published in 1914, his first in this journal in 1918, and his most recent in 1984. These 70 years saw the production of 210 articles and four books. Within the past few months a full-length biography (PROVINE 1986) has appeared, along with a reprint of some of WRIGHT's best and hardest-to-obtain papers (WRIGHT 1986). Furthermore, his four-volume treatise on population and evolutionary genetics is now available in paperback form (WRIGHT 1968, 1969, 1977, 1978). It seems timely and fitting to make him the subject of this first "Perspectives."

WRIGHT's writings in mathematical population genetics, inbreeding, and evolutionary theory are known to all geneticists and his inbreeding coefficient is a standard part of elementary courses. Yet he devoted the major share of his time to physiological and developmental genetics, and this work is much less known. He worked on pigment genetics of guinea pigs from his graduate student days until his retirement from the University of Chicago in 1955, and produced a stream of papers from 1916 to 1960. He also studied a number of developmental problems. He sometimes thought of switching to the mouse or Drosophila, but there were always more guinea pig experiments to do.

I recently asked WRIGHT how he happened to choose the guinea pig. He replied that he did not choose it; it was assigned to him by WILLIAM E. CASTLE, his mentor at Harvard. C. C. LITTLE had started graduate work earlier in the same laboratory and was already working on mice. CASTLE himself worked with rats and rabbits. I have often wondered how different the history of genetics in the United States might have been had WRIGHT and LITTLE arrived at Harvard in reverse order. Surely the early work on mouse genetics would have been more chemical and physiological, and there would have been much greater emphasis on gene interaction. LITTLE emphasized the development of inbred lines and the study of transplantable tumors. Their most striking contrast, however, was personal. WRIGHT was, and is, shy and retiring. LITTLE was a politician and organizer. After being fired as President of the University of Michigan, he was able, through persistence and personal charm, to raise enough money to found the Jackson Laboratory in Bar Harbor, Maine, now a world center for mouse genetics. Guinea pigs would have been much less suitable. In any case, the genetics world owes a vote of thanks to the trustees of the University of Michigan for unintentionally starting a great research laboratory.

WRIGHT published an extensive review of physiological genetics in 1941 (WRIGHT 1941a). He planned to expand it into a book, but this was also the year that biochemical genetics of Neurospora began (BEADLE and TATUM 1941). WRIGHT foresaw that this would forever alter the nature of genetical research and abandoned his project as *passé*. Perhaps it is time to resurrect WRIGHT's kind of quantitative studies of gene action and interaction, utilizing the enormous advances in molecular genetics and changed viewpoints since that time.

At the 1932 International Congress of Genetics, H. J. MULLER (1932) showed how, by judicious use of deletions and duplications to vary gene dosage, he could classify mutant gene action relative to that of the normal allele. He introduced the words that are now part of the standard vocabulary of genetics: *amorph* (producing a phenotypic effect equivalent to that of a deletion), *hypomorph* (producing an effect like that of the normal allele, but weaker), *hypermorph* (stronger than the normal allele), *antimorph* (producing an effect antagonistic to that of the normal allele), and *neomorph* (producing a new effect). It is to MULLER's credit that he did not speculate about intermediate mechanisms, knowing that the only available information came from external phenotypes. In the MULLER tradition, but using newer techniques, is an article in this issue (BARTON, SCHEDL and KIMBLE 1987).

By 1939, having quantitative chemical and colori-

metric information on guinea pig coat pigments, WRIGHT was able to carry MULLER's analysis further. Using then-current theory of enzyme kinetics, he derived a series of differential equations from which various interactions caused by dominance and epistasis could be inferred (WRIGHT 1941b). For example, he pointed out an addition to MULLER's classes—a *mixomorph*, an allele that acts as a hypomorph with respect to less active alleles, but as an antimorph with respect to more active ones. This, WRIGHT suggested, would happen if the mutant gene product were effective in combining with the substrate but ineffective in producing the product of the reaction. Such a mutant, *pearl* eye color (w^p), was in fact found in Drosophila by A. STEINBERG and studied by a puzzled GOLDWEBER (1939). In combination with an amorph, *white* (w), and a hypomorph, *eosin* (w^e), the genotypes in order of eye pigmentation are

$$ww < w^pw < w^pw^p < w^ew^p < w^ew < w^ew^e.$$

Thus, w^p increases the pigment in combination with the amorph w, but decreases it in combination with the hypomorph w^e, as a mixomorph should.

WRIGHT earlier had observed that alleles at the *C* locus, which affects coat and eye color in the guinea pig, could not be arrayed in a single order when both yellow and black pigments were considered. But, by using a complex model involving two substrates and interacting genes, WRIGHT was able to assign numbers to individual reaction-rate constants and predict *quantitatively* the pigment measures of genotypes involving alleles at six loci. It represented a major *tour de force* in quantitative physiological genetics, and represents a high point for this kind of model building. Yet it has received little attention. I might note that both MULLER's and WRIGHT's articles are now hard to find, although part of MULLER's has been reprinted (1962).

WRIGHT's later work (1960 and references therein) was more quantitative in the measurements and more sophisticated in the statistical analysis, but the story got to be too complicated for a single overall quantitative interpretation. As the biochemical information becomes more precise, we can expect to add mechanistic details to WRIGHT's kind of analysis. He could only measure phenotypes; now intermediate products can be taken into account. For example, KACSER and BURNS (1981) have continued in the WRIGHT tradition to explain the ubiquity of dominance, using a "sensitivity coefficient" defined as the ratio of the proportional changes of flux and enzyme activity.

One more example, this time showing the continuing relevance of WRIGHT's experimental work: KINGHORN (1987) has developed an analysis that combines molecular models of polymer formation with traditional analysis of epistatic variance components. And where did he go for the best data on life history and production traits? To WRIGHT's guinea pig measurements published in 1922 (WRIGHT 1922a,b).

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JAMES F. CROW
Genetics Department
University of Wisconsin
Madison, Wisconsin 53706