

# Perspectives

## Anecdotal, Historical and Critical Commentaries on Genetics

*Edited by James F. Crow and William F. Dove*

### Ira Herskowitz: 1946–2003

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AS a rule, we geneticists do not pay very much attention to intellectual history. Occasionally something happens that causes us to think, if only briefly, about the intellectual roots of our science. One such event was the premature death of Ira Herskowitz in April of 2003 at the age of 56. Through his scientific discoveries, and the uniquely elegant and effective way in which he conveyed them in person and in print, Ira had a profound and formative effect on the way in which all biologists today think about and describe genetic regulatory circuits and mechanisms.

Ira had a great ear for colloquial language, especially the language of sports. So it is appropriate to sum up his career by saying that from its very beginning to its premature end, Ira was a franchise player in the major leagues of genetics. Not everybody will remember that, while still a graduate student, Ira contributed one of the major pieces to our understanding of the logic of regulation in the bacteriophage  $\lambda$ . Ira's phage work established him as a pioneer in molecular genetics.  $\lambda$  (Figure 1) was the first organism whose regulatory strategies became well understood; the themes and lessons of  $\lambda$  genetics resonate in all of modern genetics. Much better known are Ira's many subsequent contributions to basic understanding of the molecular genetics of *Saccharomyces cerevisiae*, which in time, partly as a consequence of Ira's work, became the premier experimental organism for eukaryotic regulatory studies.

Any description of the basis for Ira's influence must take into account his extraordinary personality and communication skills. Ira was legendary for the clarity and humor with which he could convey often complicated ideas and experimental results. But this observation does not begin to convey his charisma. Ira loved music and loved to perform, especially his twin brother Joel's composition "The Double-Talking Helix Blues," com-

posed while the twins were still students. He also wrote his own songs, which contained perceptive and witty vignettes of life in the major leagues of academic science in the late twentieth century. Ira occasionally performed these songs at meetings, especially in later years. Everybody looked forward to them, even though we knew all the words already. So it was with lectures; Ira's skill in delivery made even the most basic or elementary ideas (the central dogma, regulation, or the *lac* operon) fresh and interesting for old pro and novice alike.

Ira was a dedicated and effective teacher all his life (Figure 2). Some of his extraordinary teaching style was derived from his egalitarian instinct and temperament and some, no doubt, from his tradition. He made personal connections and talked as easily with the dishwasher or janitor as he did with the graduate student or professor. Ira's tradition was academic genetics: his father Irwin was a *Drosophila* geneticist (a former student of H. J. Muller, who in turn had studied with T. H. Morgan), well known for his teaching and a successful college-level genetics textbook. Ira excelled in talking to nonscientists and students, but he also had a special knack for finding new ways of making the value of genet-



FIGURE 1.—Phage.

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ics clear to biochemists. More than one of his colleagues in the Department of Biochemistry and Biophysics at the University of California at San Francisco (UCSF) has remarked that Ira made geneticists of them all. His papers, especially his reviews (discussed later), were, like his songs, works of art. The scientific content, sometimes confusing even for geneticists, was always enhanced by Ira's gift for creative and effective ways of describing complexity simply and elegantly.

#### BACTERIOPHAGE $\lambda$ : THE LATE OPERON AND POSITIVE CONTROL

Ira Herskowitz defended his Ph.D. thesis at the Massachusetts Institute of Technology (MIT) in 1971. It contained the substance of several papers that have had enduring impact. Ira entered graduate school in 1967, after completing his undergraduate work at Caltech, an experience which, he often said, left him ambivalent. On the one hand, Caltech was something of a struggle for Ira, as it was for many students during the 1960s, especially those who were not strongly mathematics oriented. On the other hand, it was at Caltech that Ira first encountered phage (in Bob Edgar's laboratory) and came under the influence of the Delbrück school (or "church," as it was sometimes called), and it was there that he was introduced (by Jean Weigle) to  $\lambda$ , his first love in science. In the best tradition of undergraduate education, Ira found his calling at Caltech.

At MIT in the 1960s, doing genetics meant one worked with phage and bacteria. The Department of Biology had recently been rebuilt around a group of senior intellectual leaders in the new science of molecular biology (notably Salvador Luria, Cyrus Levinthal, Boris Magasanik, Maurice Fox, and Alexander Rich), who recruited in turn a number of younger scientists with similar interests (including David Baltimore, Harvey Lodish, Paul Schimmel, Ethan Signer, and me). Ira, wanting to build on his Caltech experience, chose to work with Ethan, who had studied with Levinthal and Sydney Brenner and whose entire laboratory was devoted to  $\lambda$ . At that time, regulation of gene expression was the major preoccupation. Negative regulation of operons by repressors had already been well established through the work of F. Jacob, E. Wollman, and J. Monod. In contrast, positive regulation by activators was still a controversial idea, although evidence for such a system had been presented by Ellis Englesberg.

Ira wrote a short memoir (HERSKOWITZ 1998) recalling how, early in his graduate career, he had become fascinated with the "functional rescue" of  $\lambda$  late gene function from a repressed prophage by superinfecting heteroimmune phages (*i.e.*,  $\lambda$ -like phages with a different repressor specificity) defective in late genes (DAMBLY *et al.* 1968) and how Ethan had suggested testing a nested series of deletion prophages for their ability to elicit this expression. The subsequent investigation (HERSKOWITZ and SIGNER 1970) defined, for the first

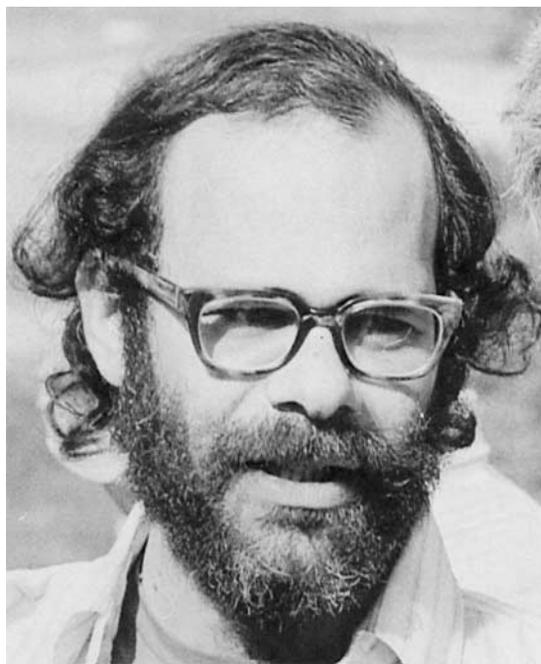


FIGURE 2.—Ira Herskowitz, 1980.

time, a regulatory site in the prophage where the product of the  $Q$  gene of the superinfecting phage must act to induce the late genes. Ira found that the site was adjacent to the  $Q$  gene, but that deletion of the prophage  $Q$  gene (along with the entire left side of the prophage, including the promoters regulated by the phage repressor) made no difference in functional rescue, establishing unambiguously that the  $Q$  gene of the superinfecting phage must be producing a diffusible activator. This result also meant that transcription of the late genes must originate from this region at or near the site of  $Q$  product action, all other known promoters having been deleted. Further, because the induction of the late genes appeared to be all or none, Ira concluded that the entire complement of  $\lambda$  late genes composes a single operon controlled by the site. Such an operon must span the ends of the linear mature  $\lambda$  genomic DNA, allowing Ira to provide a very convincing argument that, after infection, late gene expression must require circularization (or end-to-end joining) of the injected  $\lambda$ DNA.

This was a plentiful harvest of strong conclusions from what really was a modest series of very well-conceived experiments. Later, Ira extended these results, showing that a substitution in the  $QSR$  region of  $\lambda$  from another lambdoid phage resulted in a new regulatory specificity with similar properties: the  $Q$  gene products from  $\lambda$  and the  $p4$  variant can each act on their adjacent sites but not on each other's sites, in perfect analogy with immunity repressors (HERSKOWITZ and SIGNER 1974). Except, of course, this was positive control, and the specificity was one of apparently proteinaceous activators as opposed to repressors for sites on the DNA.

All of the preceding was described in just the first two

of the six substantive chapters of Ira's thesis. Succeeding chapters described the activities of additional positive regulators in  $\lambda$ : the products of the *N*, *dII*, and *dIII* genes. The latter occupied Ira and his group for many years, and I will return to them later.

#### GENE INTERACTIONS: *gro*<sup>-</sup> MUTANTS

The sixth chapter of Ira's thesis describes an entirely different line of investigation, one that was to have comparable influence on molecular genetics in the future. This was a collaboration with Costa Georgopoulos, who had recently obtained his Ph.D. at MIT for thesis work done on the glycosylation of phage T4 DNA with S. E. Luria. Costa had applied to work as a postdoctoral fellow with Dale Kaiser at Stanford, then a major center for  $\lambda$  research, but there was no bench space in Kaiser's laboratory for about a year. Costa asked Luria if he might remain in Luria's MIT laboratory and begin to learn more about  $\lambda$ . It says a lot about science in those days that Luria agreed to this as a matter of course. It went without saying that the source of  $\lambda$  learning at MIT was Ethan Signer's laboratory (which was on the same floor as Luria's) and, more specifically, Ira Herskowitz.

Ira and Costa came up with an experimental rationale and design that had far-reaching consequences, as an intellectual approach and as a fertile source of interpretable genetic interactions, through the discovery of genes that encode proteins of a kind (molecular chaperones) that had previously not even been suspected. The idea was simple: it seemed obvious that host genes and proteins participate in intracellular processes that are essential for phage propagation, such as transcription and DNA replication. Ira and Costa set out to find mutations in such host genes that had lost their ability to participate in the phage process. They adapted a variant of a then already standard technique referred to as the "nibbled colony" method in which single colonies of phage-sensitive bacteria are "nibbled" as they grow up by phages that previously had been spread on the plates. To circumvent the straightforward reasons for host resistance (loss of surface receptors and immunity), they used a mixture of phage types, and they applied numbers of phages too small to kill cells when they first were plated, but large enough to strongly inhibit the growth of colonies thereafter. The large colonies that emerged from this screening procedure were called *gro*<sup>-</sup> mutants.

It was at this point that the real inspiration came. Ira and Costa plated  $\lambda$  on each of these mutant hosts and were rewarded, in a number of cases, with  $\lambda$  mutants that again had the ability to grow. It was also here that "chance favored the prepared mind" (or that Delbrück's "principle of limited sloppiness" came into play): they had done the screen in an *Escherichia coli* strain that carried the nonsense suppressor *supE*, and many of the  $\lambda$  mutants that they recovered turned out to be *amber* mutants. This simplified greatly the subsequent genetics. Ira's complementation testing and mapping of these

$\lambda$  mutants showed that, for some of the *gro*<sup>-</sup> bacterial strains, the phage mutations fell into a single gene. Ira pursued one class of these bacterial mutants, *groP*<sup>-</sup>, which were named for the property that the  $\lambda$  mutants ( $\pi$ ) that grow on this strain fall into the  $\lambda$  *P* gene, and Costa (now already at Stanford) also pursued *groN*<sup>-</sup> and *groE*<sup>-</sup> mutants, analogously defined. In short order, Ira and Costa each had shown, by genetic means, that the failure to grow in the *groP*<sup>-</sup> or *groN*<sup>-</sup> host was the failure of  $\lambda$  *P* or *N* function, respectively, during infection. Even more importantly, a short time later, each had identified the host gene involved: one of the *groP*<sup>-</sup> genes turned out to be the essential host DNA replication gene *dnaB*, and the *groN*<sup>-</sup> gene turned out to encode the  $\beta$ -subunit of *E. coli* RNA polymerase.

These studies (GEORGOPOULOS and HERSKOWITZ 1971; GEORGOPOULOS 1971a,b) are essentially the first examples in which functional interactions between genes (or proteins) could be straightforwardly and unambiguously inferred from purely genetic arguments. The work was simplified, both experimentally and with respect to interpretation, by the fact that the host and phage have separate genomes. The genes in question ( $\lambda$  genes *P* and *N* and the host genes *dnaB* and *rpoB*) are essential to growth, and some notion of function for each of them existed already on the basis of mutant phenotypes. The lasting effect of these articles was a strong affirmation that the genetic interaction game (finding mutants that do not do something and recovering second-site mutants that recover this function) could be broadly applicable, interpretable, and fertile, even under less simple circumstances, and could be managed even for genes essential to survival. Further, many of the host genes (notably *groE*<sup>-</sup> and a trio of additional *groP*<sup>-</sup> genes (now known as *dnaJ*, *dnaK*, and *grpE*) turned out to define a new class of protein, the molecular chaperones, whose function is to facilitate protein folding and/or to control the formation and dissociation of protein complexes. This field has grown massively, and its importance has risen steadily since it began as a collaboration between a graduate student and a postdoc (see FRYDMAN 2001 and SLAVOTINEK and BIESECKER 2001 for recent reviews).

Thus Ira, in his Ph.D. thesis, made seminal contributions to two major intellectual ideas that have animated molecular genetics since: inference, by well-designed genetic studies, of regulatory mechanism, on the one hand, and inference of gene and/or protein interactions on the other. Readers interested in the latter point may find the discussion of mechanisms in GEORGOPOULOS and HERSKOWITZ (1971) surprisingly prescient.

#### COMMUNICATING REGULATORY RELATIONSHIPS: THE T-BAR AND THE ARROW

Ira came early to the business of writing about genetics for a broad audience. Already in high school, he had indexed and proofread his father Irwin's textbook,

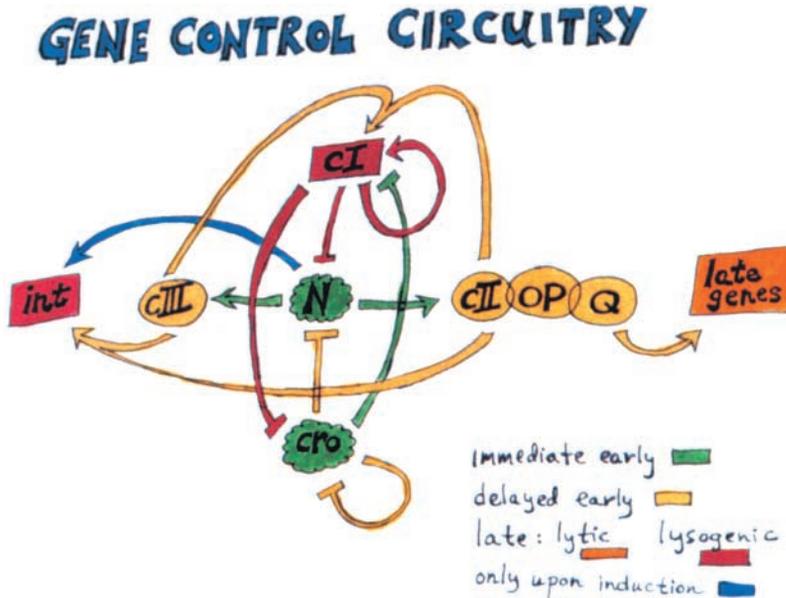


FIGURE 3.—Summary diagram from a slide used by Ira in his lectures, ca. 1980.

and, by all accounts, had improved it in other nontrivial ways. He spent the summer of 1968 at Cold Spring Harbor, becoming accepted as a peer by the famous and highly competitive group of more senior “*lambdologists*” who gathered there in the summer. He later was invited to spend a few months at the Institut Pasteur, another hotbed of  $\lambda$  research presided over at that time by Harvey Eisen and, of course, François Jacob. Ira attended the extraordinary meeting in September of 1970 that resulted in the famous and ultimately authoritative monograph “The Bacteriophage Lambda,” edited by Al Hershey, in which the *groP*<sup>-</sup> and *groN*<sup>-</sup> articles (GEORGOPOULOS and HERSKOWITZ 1971; GEORGOPOULOS 1971a) were published. The *groP* story was published nowhere else: Ira treasured Hershey’s handwritten review of this article: “Written with clarity and care” and signed simply “Al.” It was no surprise that Hershey chose Ira to index and proofread (and, of course, suggest improvements to) the book. Ira also produced its excellent glossary. One of Ira’s improvements was the inclusion of a list of “Lambda Genetic Elements” (SZYBALSKI and HERSKOWITZ 1971) that helped everyone reading the book connect discussions in the articles to the genetic and physical maps.

This experience, and the urging of the readers of his thesis, resulted in the first of Ira’s two influential reviews of  $\lambda$  genetics (HERSKOWITZ 1973; HERSKOWITZ and HAGEN 1980). These won him one of his proudest honors, the 1985 National Academy of Sciences Award for Excellence in Scientific Reviewing. These reviews remain the most comprehensible expositions of the essential elements of  $\lambda$  regulation. They, along with the aforementioned monograph, are the permanent record of what we ultimately understood, in the pre-DNA sequence era, about regulation from genetic studies of this best-studied genetic organism.

It was about this time that Ira began to develop his unique style of blackboard and slide presentations. At first these were just elaborate arrows and drawings that could be characterized as elegant doodles; but in time they became not only a feature of Ira’s style, but also an increasingly effective communication technique. Ira’s 1973 review contained the first of these “Ira-grams” to be published (see HERSKOWITZ 1973, Figure 7). A later version of this diagram is shown in Figure 3. Here Ira displays his mature diagramming style and has incorporated his signature innovation, the use of arrows to indicate stimulatory action (or positive control) and the T-bar to indicate inhibitory action (or negative control). In the 1973 version, both kinds of regulation were shown with arrows. The T-bar makes the diagram very much easier to understand. It is no wonder that it has come into universal favor and is now to be found wherever genetic regulation or signal transduction relationships are described.

The diagram offers an opportunity to summarize Ira’s contributions to the understanding of the regulatory circuitry of  $\lambda$  (see HERSKOWITZ and HAGEN 1980 for detail and references). At the extreme right of Figure 3, the arrow shows positive control of late gene transcription, Ira’s first important contribution. Ira also contributed, in his own laboratory in Oregon and later in San Francisco, to the full understanding of the positive regulatory actions of *cII* and *cIII* and to understanding the central role of the positive regulator *N* on both rightward and leftward transcription. And, not least, Ira had a considerable role in elucidating the several regulatory roles of *cro* (all negative) and *cI* (some negative and some positive) on themselves and each other. What is remarkable is how easily the T-bars and the arrows in Figure 3 allow the reader to follow the complexity of these circuits.

Ira's lasting interest in  $\lambda$  concerned the way in which these already complicated circuits respond to signals from the bacterial host. Ira's diagram of this (Figure 4) emphasizes the central role of *cII* in this regard. The host Hfl function responds to the level of cyclic AMP, which is a measure of nutritional status of the cell. Hfl is a negative regulator of *cII*, which in turn has an overall inhibitory effect on lytic growth and a stimulatory role on lysogenization functions [repressor (*cI*) expression and *int*]. *cIII* has a negative effect on *hfl* (which Ira's group eventually traced to proteolysis), and the circuit is complete.

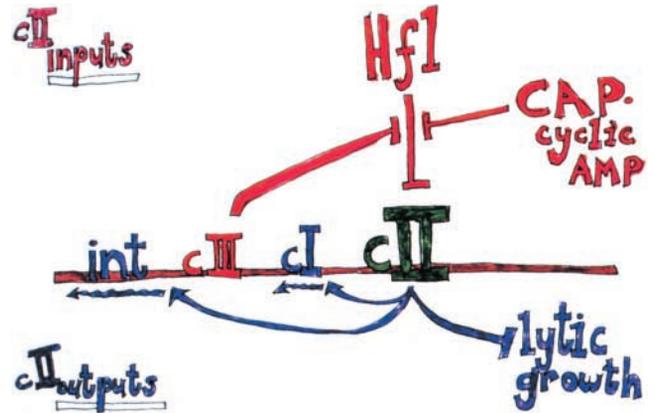


FIGURE 4.—Host influence on the lysis-lysogeny decision.

#### BRINGING $\lambda$ -STYLE GENETIC ANALYSIS TO THE STUDY OF GENE REGULATION IN YEAST

While still a graduate student, Ira was offered, and accepted, a position as assistant professor in the Molecular Biology Institute at the University of Oregon. Nobody was surprised that this nest of major figures in phage biology (including Frank Stahl, George Streisinger, and Aaron Novick) would make such an appointment, given Ira's accomplishments, even though they were still largely unpublished. However, feeling a little unprepared, Ira asked for a year's delay, which he spent in my laboratory at MIT. Ira and I decided to spend that year learning something new together. We took the Yeast Course at Cold Spring Harbor, which had been inaugurated by Gerry Fink and Fred Sherman the previous year (see SHERWOOD 2001). Elsewhere (BOTSTEIN 1993) I have described some of our ideas and motivation for choosing yeast. I also describe (BOTSTEIN 1993) how impressed I became with Ira as a teacher when he managed to teach me, a nearly total nonathlete, enough table tennis to be regarded as dangerous at Gordon Conferences. The secret, he said, was to "do the same in Ping-Pong as in genetics. Focus on the fundamentals and you'll do all right." After we returned to Cambridge, we started to work with yeast and did a little phage work on the side (eventually published as BOTSTEIN and HERSKOWITZ 1974). Ira had an appointment as an instructor, and together we taught a Project Laboratory course in which Ira once again distinguished himself as an extraordinarily effective and memorable teacher, this time in the laboratory.

Almost from the first, Ira became fascinated with the mating system in *Saccharomyces*. He was especially intrigued by an article by TAKANO and OSHIMA (1970) that showed apparently mutational conversion of mating types in yeast. We spent many hours discussing the differences in frequency and consequences of forced matings between two **a** or two  $\alpha$  strains. Ira's fascination soon turned to insight. One day Ira wrote a table on the blackboard in my office in which, for the first time in my memory, he distinguished **a** (or **a/a**),  $\alpha$  (or  $\alpha/\alpha$ ), and **a**/ $\alpha$  diploid cells as three different cell types. He included under the heading for each type a list of

functions that must be different for each type, and he began to talk about studying the regulation that must underlie these cell-type differences. Just as he had discovered  $\lambda$  at Caltech, Ira decided at this time that he would focus his yeast research interests on the cell-type differentiation problem, which he already saw as a problem analogous in many ways to the lysis-lysogeny problem in temperate phages. This became the underlying theme of all his subsequent work.

By all accounts, Ira's arrival in Oregon the next year was memorable. So attractive was the intellect, style, and enthusiasm of this beginning assistant professor that a number of students soon abandoned their perfectly good projects in other laboratories and began to work with Ira. Within a year he had several students working on both phage and yeast. Notable among these were Jim Hicks and Jeff Strathern, soon to be joined by Jasper Rine. With this able group of students, Ira set out to understand the regulatory circuits associated with mating and cell type in *Saccharomyces*.

#### MATING-TYPE INTERCONVERSION

The first success of this group was the elucidation of the mechanism by which the mating types switch in homothallic strains. Once again, a classic diagram of Ira's (Figure 5) makes the outline of this idea clear at a glance. The critical feature of this mechanism (HERSKOWITZ and OSHIMA 1981; RINE *et al.* 1981) is the idea that when there is switching, the information at the *MAT* locus is discarded, and a copy of one of the silent loci (*HMR* in Figure 5) is substituted. This feature was the basis for the critical experimental distinction between this and a true "switching" mechanism, involving an alternation of the same information. That critical experiment Ira called the "healing experiment," wherein a mutation at the *MAT* locus rendering the cell sterile is "healed" by a sequence of two mating-type switches. Once again, the Ira-gram says it all succinctly (Figure 6). An even more elaborate (and, arguably, even

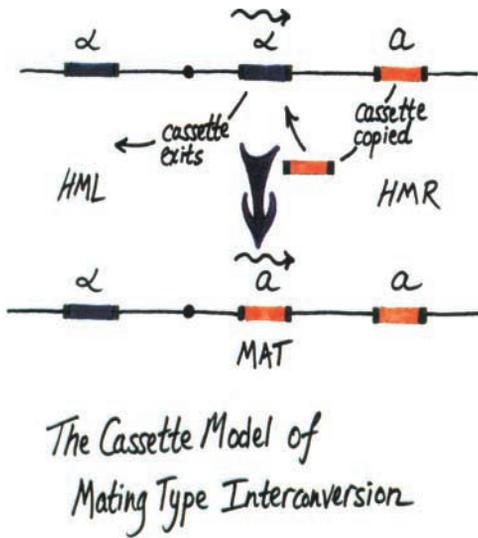


FIGURE 5.—Ira’s diagram of the cassette model of mating-type interconversion.

more critical) tour de force was the “wounding experiment,” in which a mutant cassette in one of the silent loci in a fertile strain caused a cell to be rendered sterile after two switches of mating type (KUSHNER *et al.* 1979).

The technology that Ira and his group employed to achieve these results was both simple and elegant. They used simple microscopy and micromanipulation together with a clever assay based on pheromone sensitivity for assessing the mating phenotype of single cells. The results of these experiments were to guide study of both cell-type determination and switching for years

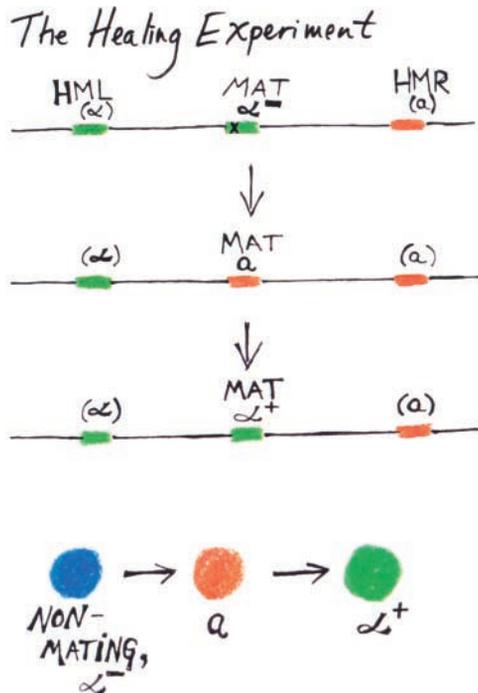


FIGURE 6.—Ira’s diagram of the healing experiment.

Analogies to Development in Higher Eukaryotes —

1. stem cell/differentiated cell population.
  - "diff. cell"
  - "stem cell"
2. Sequential cassette insertion-
  - i. cassettes *cas A*, *cas B*, etc determine cell types A, B, C...
  - ii. *cas A* codes for function which directs insertion of *cas B*, etc.

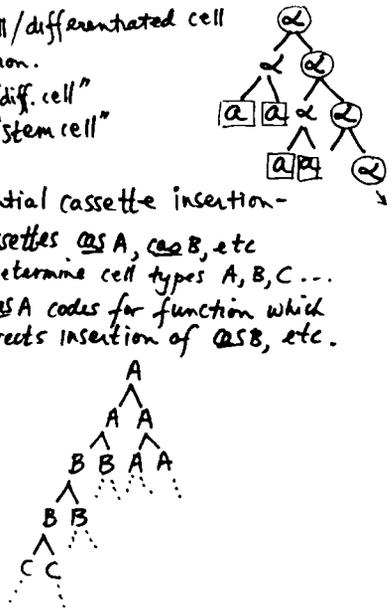


FIGURE 7.—Ira’s diagram of analogies to development in higher eukaryotes.

to come. One of the major results, however, was the establishment of the fundamental asymmetry of cell division in yeast (STRATHERN and HERSKOWITZ 1979), which led Ira to propose a generalization that has had considerable influence in the larger world of cell biology. This is summarized in Figure 7.

Finally, of course, Ira’s Oregon period was capped by the derivation and ultimate success of the  $\alpha 1$ - $\alpha 2$  hypothesis (Figure 8), which was the result of a long study of regulatory mutants isolated by Ira’s group at the *MAT*

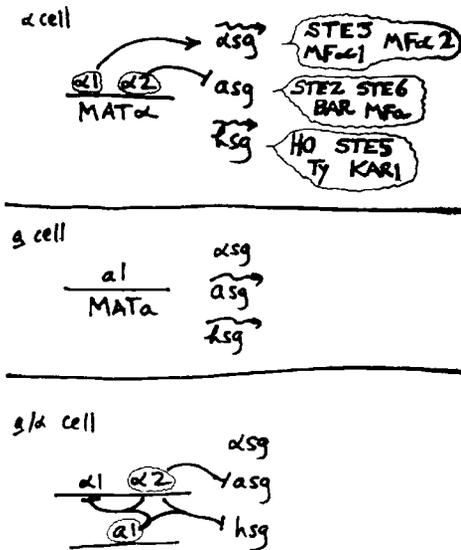


FIGURE 8.—The  $\alpha 1$ - $\alpha 2$  hypothesis.

locus. The hypothesis describes strikingly  $\lambda$ -like regulatory circuitry that allows yeast to produce the three cell types under the control of the genes defined by these mutants (STRATHERN *et al.* 1981). This system is probably still the best-understood regulatory system in eukaryotic biology and today is taught in every textbook of genetics and cell biology, alongside the lysis-lysogeny decision of  $\lambda$  and the *lac* operon of *E. coli*. Here Ira achieved his goal: he brought  $\lambda$ -style molecular genetics to yeast, used it to understand a complex eukaryotic regulatory system, and explained it all to the world.

#### THE AWESOME POWER OF YEAST GENETICS AT UCSF

After 10 productive years at Oregon, Ira moved to the Department of Biochemistry and Biophysics at the University of California, San Francisco. Basic science at UCSF then was dominated by intellectually powerful figures in biochemistry and cell biology, microbiology, and virology. Ira brought to UCSF a similar power in genetics. He once told me that he moved to UCSF after a sabbatical there convinced him that he would be able to think more broadly about more diverse science at UCSF. He also thought he could have an impact by bringing the power of genetics to that diverse science, and possibly even to medicine. As usual, Ira had the right instinct, for, as I have already indicated, he “made geneticists of them all.” At UCSF he contributed repeatedly to the science of others, faculty and students alike, by encouraging them to think genetically. An interesting publication that came out of such discussions is Ira’s influential note (HERSKOWITZ 1987) pointing out the potential value of overexpressing dominant-negative mutant proteins in systems, such as mammalian cell culture, in which standard genetic approaches are not practical. This suggestion has, of course, more than stood the test of time; it, too, has become a standard method and appears in all the textbooks. Note that, in contrast to many, Ira’s San Francisco colleague Marc Kirschner got the dominant-negative approach right by distinguishing between the “antimorph” and the “neomorph” through titration by wild type (AMAYA *et al.* 1991).

It is tempting to continue to chronicle Ira’s contributions. However, as we come closer to the present, Ira’s contributions are actually much better known, and only a mention seems necessary. Among the highlights are his classic studies on cell polarity, originally motivated, once again, by Ira’s interest in the differences among the yeast cell types and how they are controlled. Among these differences are the budding pattern (new buds in **a** and  $\alpha$  cell types emerge adjacent to the previous bud, whereas **a**/ $\alpha$  buds emerge at the opposite pole). By isolating and analyzing mutations that alter the budding pattern, Ira’s group discovered how eukaryotic cells establish and maintain asymmetry (CHANT *et al.* 1991; CHANT and HERSKOWITZ 1991), involving proteins and

a mechanism that is largely conserved in mammalian cells as well.

In his last years, like many others of us, Ira became impressed with how slow the evolution of proteins and signal transduction systems has been, and how closely related, in their basic cell biology, all eukaryotes remain. This led him to pursue the possibility that yeast, now well established as a model system for genetic regulation and cell biology, could be used to screen for and to understand the activities of chemical agents. He sought to bring the “awesome power of yeast genetics,” a power he did more than anybody else to establish, more directly into the practice of medicine through pharmacology. He did not live long enough to accomplish this last of his big goals, but his track record in choosing such goals should give pharmacogenetics advocates considerable comfort.

I hope that readers who did not know Ira Herskowitz, or who know him only from his later works, will see how Ira’s career was a coherent whole, animated by a life-long set of intellectual interests and goals that had their origins in his earliest work on regulation in  $\lambda$ . He had, more than any of his peers, the gift for pushing back the frontier of science with simple experiments ably conceived, which somehow always got to the heart of the issues with a minimum of fuss and with no unnecessary technology. He clarified every problem he addressed and made the solution as well as the problem clear to everyone. In April 2003, the science of genetics lost one of its very best.

I am grateful to many of Ira’s colleagues for their help with this essay, especially Costa Georgopoulos, Jasper Rine, and Gerry Fink, who read the manuscript, corrected some of my errors, and made many useful comments. Jasper found the slides from which the illustrations were made among Ira’s papers. Jeff Strathern and Pinky Kushner helped me try to find (somewhat inconclusively) Ira’s first use of the T-bar and the arrow. Douglass Forbes was kind enough to provide, in a very short time, a copy of Ira’s Ph.D. thesis.

#### LITERATURE CITED

- AMAYA, E., T. J. MUSCI and M. W. KIRSCHNER, 1991 Expression of a dominant negative mutant of the FGF receptor disrupts mesoderm formation in *Xenopus* embryos. *Cell* **26**: 257–270.
- BOTSTEIN, D., 1993 A phage geneticist turns to yeast, pp. 361–373 in *The Early Days of Yeast Genetics*, edited by M. N. HALL and P. LINDER. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- BOTSTEIN, D., and I. HERSKOWITZ, 1974 Properties of hybrids between *Salmonella* phage P22 and coliphage lambda. *Nature* **251**: 584–589.
- CHANT, J., and I. HERSKOWITZ, 1991 Genetic control of bud site selection in yeast by a set of gene products that constitute a morphogenetic pathway. *Cell* **65**: 1203–1212.
- CHANT, J., K. CORRADO, J. R. PRINGLE and I. HERSKOWITZ, 1991 Yeast BUD5, encoding a putative GDP-GTP exchange factor, is necessary for bud site selection and interacts with bud formation gene *BEM1*. *Cell* **65**: 1213–1224.
- DAMBLY, C., M. COUTURIER and R. THOMAS, 1968 Control of development in temperate bacteriophages. II. Control of lysozyme synthesis. *J. Mol. Biol.* **32**: 67–81.
- FRYDMAN, J., 2001 Folding of newly translated proteins in vivo: the role of molecular chaperones. *Annu. Rev. Biochem.* **70**: 603–647.

- GEORGOPOULOS, C. P., 1971a A bacterial mutation affecting *N* function, pp. 639–645 in *The Bacteriophage Lambda*, edited by A. D. HERSHEY. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- GEORGOPOULOS, C. P., 1971b Bacterial mutants in which the gene *N* function of bacteriophage lambda is blocked have an altered RNA polymerase. *Proc. Natl. Acad. Sci. USA* **68**: 2977–2981.
- GEORGOPOULOS, C. P., and I. HERSKOWITZ, 1971 *Escherichia coli* mutants blocked in lambda DNA synthesis, pp. 553–564 in *The Bacteriophage Lambda*, edited by A. D. HERSHEY. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- HERSKOWITZ, I., 1973 Control of gene expression in bacteriophage lambda. *Annu. Rev. Genet.* **7**: 289–324.
- HERSKOWITZ, I., 1987 Functional inactivation of genes by dominant negative mutations. *Nature* **329**: 219–222.
- HERSKOWITZ, I., 1998 Coming early to the late genes. *Curr. Biol.* **8**: R827–R828.
- HERSKOWITZ, I., and D. HAGEN, 1980 The lysis-lysogeny decision of phage lambda: explicit programming and responsiveness. *Annu. Rev. Genet.* **14**: 399–445.
- HERSKOWITZ, I., and Y. OSHIMA, 1981 Control of cell type in *Saccharomyces cerevisiae*: mating type and mating-type interconversion, pp. 181–209 in *The Molecular Biology of the Yeast Saccharomyces: Life Cycle and Inheritance*, edited by J. N. STRATHERN, E. W. JONES and J. R. BROACH. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- HERSKOWITZ, I., and E. R. SIGNER, 1970 A site essential for expression of all late genes in bacteriophage lambda. *J. Mol. Biol.* **47**: 545–556.
- HERSKOWITZ, I., and E. R. SIGNER, 1974 Substitution mutation in bacteriophage lambda with new specificity for late gene expression. *Virology* **61**: 112–119.
- KUSHNER, P. J., L. C. BLAIR and I. HERSKOWITZ, 1979 Control of yeast cell types by mobile genes: a test. *Proc. Natl. Acad. Sci. USA* **76**: 5264–5268.
- RINE, J., R. JENSEN, D. HAGEN, L. BLAIR and I. HERSKOWITZ, 1981 Pattern of switching and fate of the replaced cassette in yeast mating-type interconversion. *Cold Spring Harbor Symp. Quant. Biol.* **45**: 951–960.
- SHERWOOD, P. W., 2001 The yeast genetics course at Cold Spring Harbor Laboratory: thirty years and counting. *Genetics* **157**: 1399–1402.
- SLAVOTINEK, A. M., and L. G. BIESECKER, 2001 Unfolding the role of chaperones and chaperonins in human disease. *Trends Genet.* **17**: 528–535.
- STRATHERN, J. N., and I. HERSKOWITZ, 1979 Asymmetry and directionality in production of new cell types during clonal growth: the switching pattern of homothallic yeast. *Cell* **17**: 371–381.
- STRATHERN, J., J. HICKS and I. HERSKOWITZ, 1981 Control of cell type in yeast by the mating type locus. The alpha 1-alpha 2 hypothesis. *J. Mol. Biol.* **147**: 357–372.
- SZYBALSKI, W., and I. HERSKOWITZ, 1971 Lambda genetic elements, pp. 778–779 in *The Bacteriophage Lambda*, edited by A. D. HERSHEY. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
- TAKANO, I., and Y. OSHIMA, 1970 Mutational nature of an allele-specific conversion of the mating type by the homothallic gene *HO*  $\alpha$  in *Saccharomyces*. *Genetics* **65**: 421–427.