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History and Philosophy of the Life Sciences

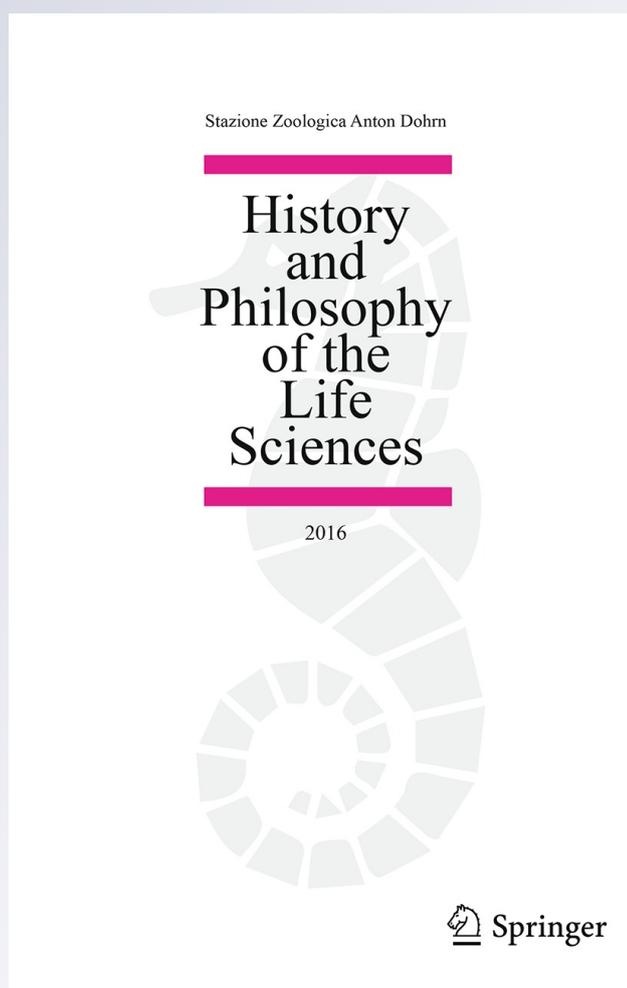
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Experimenting with sex: four approaches to the genetics of sex reversal before 1950

Michael R. Dietrich¹

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Abstract In the early twentieth century, Tatsuo Aida in Japan, Øyvind Winge in Denmark, Richard Goldschmidt in Germany, and Calvin Bridges in the United States all developed different experimental systems to study the genetics of sex reversal. These locally specific experimental systems grounded these experimenters' understanding of sex reversal as well as their interpretation of claims regarding experimental results and theories. The comparison of four researchers and their experimental systems reveals how those different systems mediated their understanding of genetic phenomena, and influenced their interpretations of sex reversal.

Keywords Sex reversal · Sex determination · Genetics · Experimental systems

1 Introduction

Tatsuo Aida (1871–1957) raised Medaka for most of his life. The little brown and grey fish were found in rice paddies and streams all over Japan. Fanciers as early as the Edo period in the eighteenth century had introduced them into garden ponds, and took note of the occasional fish with a splash of red, orange, or white (Kinoshita et al. 2009; Hori 2011, p. 3). These bright new varieties were bred and circulated among Medaka enthusiasts in the early twentieth century, when Aida began his own ponds.

As an instructor at the Kyoto Technical High School, Aida saw an opportunity to combine his interest in raising Medaka and the new science of genetics. Aida had earned a degree in zoology from Tokyo Imperial University in 1896, and established himself as a specialist in marine invertebrates as a college instructor in Kumamoto

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(Komai 1958). Beginning in 1913, Aida turned his attention to the colors of Medaka as Mendelian traits: as discrete pairs of characters that corresponded to combinations of discrete genes. Over the next 7 years, Aida performed hundreds of matings with the color varieties of Medaka in order to establish that they followed Mendelian patterns of inheritance. Mendelian genetics was growing in popularity among Japanese biologists, and Aida's discovery, by itself, was really not a novel achievement when he published his paper in *Genetics* in 1921 (Aida 1921; Ishiwaru 1917; Toyama 1916; Onaga 2015; Iida 2009, 2015). What caught Aida's attention, and that of other biologists around the world, was that Aida had discovered that the sex chromosomes seemed to be exchanging color genes. Aida had established that female Medaka carried two X chromosomes, and male Medaka carried an X and a Y chromosome. He had also established that white color was recessive and red color was dominant. With these principles, Aida arranged a set of matings that should have produced all white females and all red males. But in his backyard ponds, Aida found two red females and a white male among his expected brood of hundreds of fish. Puzzled by these three oddities, Aida postulated that there had been an exchange of the red gene from the Y to the X chromosome—something that had never been observed or even thought possible, because the X and Y chromosomes were assumed to be too different from each other to allow exchange.

Geneticists are trained to treasure their exceptions and oddities (Bateson 1908)—this is what drew Aida to those colorful fish. For the next 9 years, he experimented with the white and red orange fish. By the time he published again in 1930, the story had become even stranger. In most animals the ratio of males to females is remarkably constant with equal numbers of both sexes. Oddly, Aida's experiments tended to produce very few males, and when he bred the few males over several generations the proportions did not remain constant—the number of males increased but did not reach 50 % (Aida 1930). Aida thought he could explain this with a bit of chromosomal dynamics called non-disjunction, where the sex chromosomes do not separate during cell division and some gametes end up with an extra X or an extra Y chromosome.

Enter Øjvind Winge (1886–1964), a Danish biologist who had been doing similar experiments with guppies. Winge had also produced broods with skewed sex ratios. His explanation, however, was radically different from Aida's. Winge proposed that some of his female guppies were not as female as some of the others. Some were sex reversals: they were chromosomally male, but had developed into fish with female bodies (Winge 1930). This not only called into question Aida's interpretation in terms of non-disjunction, it destabilized the equation of chromosomal constitution with bodily sex and raised foundational issues about the nature of sex and what it meant to experimentally produce its reversal.

By 1936, Aida accepted that his Medaka had undergone sex reversal, but, as we shall see, his understanding of sex reversal had important differences from that of his European colleagues (Aida 1936). Aida now found himself in dialogue with Winge in Denmark, Richard Goldschmidt (1878–1958) in Germany, and Calvin Bridges (1889–1938) and others in the United States. All were pursuing research programs on the genetics of sex reversal and sex determination, but each had built a different experimental system using different organisms.

An experimental system encompasses how a researcher constitutes a scientific object and creates a means of interacting with the world. Experimental systems generate differences that can be marked and thereby initiate a chain of inscriptions leading to a representation of the scientific object (Rheinberger 1992a, b, 1997). Aida, his Medaka, his set of pools in his backyard, and the ways in which he managed their mating and growth all constituted an experimental system that Aida both created and was a part of as he tried to create and mark differences, like the white male fish reported in 1921. Aida's experimental system transformed his Medaka from beautiful fish to objects of genetic analysis. While this system became Aida's means of experimental interaction with the world and allowed him to generate scientific knowledge, the system was powerfully constraining. Hans-Jörg Rheinberger makes this point through Francois Jacob, who wrote: "In biology, any study thus begins with the choice of a 'system.' On this choice depends the experimenter's freedom to maneuver, the nature of the questions he is free to ask, and even, often, the type of answer that he can obtain" (Quoted in Rheinberger 1997, p. 25). Aida's system was built to generate specific kinds of differences and marks that he thought would address specific genetic questions. If he wanted to ask different questions or constitute other kinds of scientific objects, he would have to build a new experimental system. But, scientists often grow comfortable with, even fond of, their experimental systems. After years of coaxing the world to work with them through an experimental system, they become personally invested in their systems.

In this essay, I trace the history of early genetic research on sex reversal through the experimental systems constituted by Tatsuo Aida in Japan, Øjvind Winge in Denmark, Richard Goldschmidt in Germany, and Calvin Bridges in the United States. While each of these researchers developed unique experimental systems, they all developed theories of genetic sex determination that rested on the relative balance of male and female determining genes in their organisms. Differences in their experimental systems, however, were reflected in how they understood sex itself, as a male–female binary or as a gradation between male and female. Their differing abilities to experimentally manipulate the sex determination process and reliably produce intersexes and sex reversals in turn influenced their proposals for the contribution and balance of sex chromosomes, autosomes, and cytoplasmic factors. These divergent and locally specific experimental systems mediated the constitution of different versions of the balance theory of sex. Disagreement was inevitable as Goldschmidt, Winge, and Aida argued that their balance theories best explained not only their own results, but the results of the other three researchers. As they weighed the pros and cons of each interpretation, the ultimate value of any theoretical interpretation rested in how well it conformed to their own experimental system and its particular constitution of the phenomena of sex, its determination, and its reversal.

2 Inventing intersexes

On July 28, 1916, Richard Goldschmidt stood before the leaders of American biology, assembled for the summer at the Marine Biological Laboratory in Woods Hole, and declared that the elementary mechanism for the "sex-problem" had been

solved (Goldschmidt 1916). With characteristic bombast, Goldschmidt proclaimed that “there is hardly another problem which has been such a playground for dilettantism, and if we look through older literature on the sex-problem we find almost as many philosophers and economists inventing sex-theories as there are biologists.” Fortunately the “absolute ignorance” of the past had been replaced by the “hopeful knowledge” secured by the facts of Mendelian inheritance and the cytological study of chromosomes. Goldschmidt was preaching to the choir, of course. Everyone in the room agreed that chromosomes provided the physical basis for heredity, and that male and female sexes were correlated with possessing either two copies of the same accessory or sex chromosome (two X chromosomes, for instance) or two different sex chromosomes (an X and a Y chromosome, for instance) (Maienschein 1984; Richardson 2013). Accepted experiments on the inheritance of sex specific traits had also established that the sex chromosomes carried sex factors involved in the determination of bodily sex.

The fact that Goldschmidt celebrated the chromosomal theory of heredity and research on the inheritance of sex-linked traits was not accidental. This research had been done by the prominent American biologist, Thomas Hunt Morgan (1866–1945), and his research group, who happened to be in the room at MBL that day (Allen 1974; Kingsland 2009). Goldschmidt was seeking common ground before articulating the point of departure for his own research. Having established the chromosomal basis for the sex-problem, he could move on to more fine-grained questions, like what are sex factors and how do they work? And “are the two sexes clean-cut alternatives and is it therefore impossible to transform one into the other, or are they nothing but limiting points of a series, which might approached each other or be interchanged?” Goldschmidt quickly mentioned the experiments that Eugen Steinach was then performing to change the sexual characteristics of animals through castration and transplantation of testis and ovaries in order to introduce his own alternative approach to experimenting with sex by genetic means (Steinach 1916; Sengoopta 1992).

As an assistant in Richard Hertwig’s laboratory in Munich, Goldschmidt had been immersed in the problem of sex determination early in his scientific career (Goldschmidt 1960; Stern 1967; Littlefield and Bryant 1980; Richmond 1986; Satzinger 2009; Klöppel 2010). Although his own work was initially on the development of nervous systems, with the rise of genetics, Goldschmidt decided to approach the topic of sex determination from a Mendelian standpoint. Using different varieties of the gypsy moth, *Lymantria dispar*, Goldschmidt discovered in 1911 that he could produce a kind of intermediate between male and female. *Lymantria* moths were usually sexually dimorphic: females were large with dark bands on white wings, while males were small with brown wings. When two distinct geographic varieties of *Lymantria* were mated, however, the offspring were not dimorphic. Instead they produced offspring with intermediate sexual characteristics. In particular, Goldschmidt’s original cross of *Lymantria* in 1911 was between a European species, *Lymantria dispar*, and an Asian species, *Lymantria japonica* (Goldschmidt 1911). When he mated Japanese female moths to European males the resulting offspring produced “normal” males and females. When he mated European females with Japanese males, however, the male offspring appeared

normal, but the females “showed in all their bodies admixtures of male characters” (Goldschmidt 1916; Dietrich 2000a). Because these offspring were intermediate between male and female, Goldschmidt realized that they were not gynandromorphs or hermaphrodites that had both male and female features. Instead, Goldschmidt called these sexual intermediates, intersexes.

Goldschmidt's early experiments with *Lymantria* established that intersexuality was hereditary when he was able to mate intersexual moths with normal moths to produce further generations with intersexual and normal offspring. Moreover, as he began to collect different strains of *Lymantria* from different regions of Germany and Japan, and then mate those with each other, he found that these matings seemed to produce different forms of intersexual offspring. Thus, the problem of understanding the genetic basis of sex determination in *Lymantria* became bound up with the study of their geographic variation. The idea that different geographic races would produce intersexes took Goldschmidt to Japan several times in order to collect *Lymantria* from different regions, where he discovered important geographic differences that supported the production of intersexes between moths from separate regions of Japan. These “geographic races” of *Lymantria*, thus, formed the material basis for a huge number controlled matings intended to reveal the genetic foundations for sex determination. Goldschmidt's work on *Lymantria* culminated in his 185-page essay in 1934 (Goldschmidt 1934). His careful study of the geographic variation in *Lymantria* across the Japanese archipelago was ground breaking research that became widely cited in the evolution literature (Goldschmidt 1940; Dietrich 1995, 2000b).

To a basic genetic experimental system that centered around the controlled mating of individuals across generations and the tracking of bodily differences from generation to generation, Goldschmidt added the systematic study of geographic varieties as manifest in the number of different forms of offspring and the degree of intersexuality produced in these sets of laboratory matings. This experimental system was created by Goldschmidt in his laboratory in Berlin, and in the United States and Japan, during visits there. The thousands of moths required for these experiments had to be kept alive for many months and in separate cages during mating season. This required both dedicated space and a dedicated staff.

Goldschmidt's interpretative explanation of sex determination rested on the idea that each individual contained “the *anlagen* for either sex” (Goldschmidt 1916, p. 709). Bodily sex was the result of a balance between male and female genetic factors that allowed the determination process to be temporally regulated. Following a suggestion from Theodosius Dobzhansky, Goldschmidt used the term “factor,” not “gene,” because he could not determine where the factor was located on the chromosome or even if it was a single gene or a cluster of genes (Goldschmidt 1934, p. 22). Following the work of many geneticists and cytologists, Goldschmidt accepted that the sex chromosomes were bearers of some of the sex factors, while non-sex chromosomes or autosomes carried others (Richardson 2013). As we will see, Goldschmidt also argued that female sex factors in *Lymantria* could be transmitted non-chromosomally through the cell cytoplasm. Which bodily sex appeared, depended on the quantitative relation between the strength of the male and female genetic factors. Each factor did not produce a unitary trait; it produced

some substance (an enzyme or hormone perhaps) in some quantity. Because quantity and rate of production could vary, the potency or valence of the factor was said to vary, to lie in a range from strong to weak. According to Goldschmidt a normal female contained a female factor (F) and was heterozygous for the male factors (Mm). Females were thus designated FMm, while males were designated FMM. If both factors in the MM pair were weak and the Female factor was strong, the female would predominate over the male and produce an intersex or even possibly a male, which appeared completely female. The balance required to produce male and female offspring depended on the strengths of the female and male factors being in the quantitative relationship represented by the following inequality: $F > M < MM$ (Goldschmidt 1934, p. 100). Each factor was postulated to produce a product, probably an enzyme or hormone, that controlled a chain of reactions. The strength of each factor was a result of how much product it produced and at what rate (Richmond 2007, p. 179). The relative strength or “valence” of each factor was further theorized as having a quantitative value, so that the differences between the relationship of male and female factors could indicate where an individual stood on a continuum from female to male with a range of intermediate intersexes. Because the production of male and female moths depended on the balance of male and female factors, Goldschmidt called his theory, the balance theory of sex.

While his views on balance did not change, Goldschmidt's ideas about the location of relevant factors on autosomes, sex chromosomes, and in the cytoplasm did shift over the course of many years of experimentation. In his initial publications on *Lymantria*, Goldschmidt defended the view that the female factors were chromosomal. By 1920, patterns of sex determination from matings of intersexes led him to postulate that seeming constancy of female factors meant that they were inherited through the cell cytoplasm and so only passed down through a maternal lineage (Goldschmidt 1923, 1927a, b, 1931, 1934). As we shall see below, after his debate with Winge, Goldschmidt would revert back to his original position and locate sex factors on the sex chromosomes.

To explain why intersexual organisms were not uniform in their expression of intersexual characteristics, Goldschmidt also proposed what he called the Time Law of Intersexuality. In his words, “An intersex is an individual, which has developed as a male (or female) up to a certain time point; from this turning point the development has continued as a female (or male). The increasing degree of intersexuality is an expression of the recession of the turning point, that is, its occurrence at an earlier stage in development” (Goldschmidt 1923, p. 91; Allen 1980). Put another way, sex was determined by a balance of reaction products produced by male and female factors (Goldschmidt 1934, p. 100). If the male and female reaction products were out of balance, then intersexes would be produced. The timing of when that imbalance was expressed depended on the relative strength of male and female factors, or the ratio of female to male products (Goldschmidt 1934, p. 102). Intersexes were, thus, mosaics in time. They did not have a mix of male and female parts, but were intermediates. Gynandromorphs and true hermaphrodites that did have a mix of male and female body parts were considered to be mosaics in space.

Goldschmidt's expression of his results in terms of a new law of nature was typical of his approach to science. Throughout all of his research, Goldschmidt consistently strove to build a unified understanding of vast arrays of biological phenomena. In his work on sex determination, he produced a multitude of technical articles on the evidence and mechanisms of sex determination in *Lymantria*, but at the same time strove to generalize his findings as laws of nature that applied from insects to humans. Moreover, Goldschmidt thought that a vital aspect of genetics was the integration of the gene with *physiological* processes of development (Allen 1974; Richmond 2007; Dietrich 2008). As would become typical of his approach, he developed an understanding of genetics that integrated heredity with the processes of development (Maienschein 1984; Richmond 1986; Gilbert 1978; Dietrich 1996, 2000a, b, c, d, 2008). Goldschmidt explicitly contrasted his approach to that of American geneticists, such as Thomas Hunt Morgan's group, whom he characterized as engaged in "static genetics" (Goldschmidt 1950). Goldschmidt's balance theory of sex determination and time law of intersexuality were intentionally framed as authoritative generalizations that extended well beyond the *Lymantria* system where Goldschmidt could produce experimental results.

3 Searching for balance

As Richard Goldschmidt was developing his *Lymantria* system, Calvin Bridges was helping lay the foundations for the most famous and perhaps most influential experimental system in the history of genetics, the *Drosophila* system created in Thomas Hunt Morgan's fly laboratory at Columbia University (Kohler 1994; Sturtevant 1965; Allen 1978). Bridges was part of the core of Morgan's fly group. Beginning as an undergraduate at Columbia University and continuing as a doctoral student and then Research Associate, Bridges helped transform *Drosophila* into a genetic technology and establish the chromosome theory of heredity and the classical theory of the gene. Bridges was a master at tracking the minute physical changes in *Drosophila* that marked some small underlying genetic mutation. In a small room at Columbia, Bridges and the Fly Group bred thousands of flies in pint-size milk bottles lined up on shelves around the room. From a few wild caught specimens, they built up a collection of mutants that became more and more apparent as the flies became inbred and maintained on such a large scale (Kohler 1994).

In 1910, Morgan had associated genes with chromosomes by performing a series of mating with *Drosophila* that tracked eye color and sex. *Drosophila* in the wild usually have red eyes, but Morgan had found a mutant white-eyed fly. Through a series of matings, Morgan followed and counted the flies with white eyes and argued that white mutant was sex-linked (Ha 2011; Richardson 2011). Because *Drosophila* were understood to have X and Y chromosomes, this meant that the color mutant was located on a sex chromosome (Morgan 1910). By 1913, Morgan had extended this kind of genetic analysis to sex determination itself, proposing that genes for maleness and femaleness resided on the different sex chromosomes, and their

quantitative relationship contributed to the genetic determination of sex (Kingsland 2009).

As a student, Bridges became an expert at determining the chromosomal location of genes using the *Drosophila* system, so that by 1915, he had identified 50 sex-linked mutations among the half a million flies that he had bred since 1910. Sex-linkage was detected by mating a female with a sex-linked mutant carried on both of her X chromosomes to a wild-type male without the mutant. Because each parent contributes one of its two chromosomes to its offspring, and females need two copies to express a mutant trait while males only need one copy to express a mutant trait on an X chromosome, the female offspring will look like their father and the male offspring will look like their mother. But, every so often, Bridges found among the regular offspring in a sex-linked cross there were daughters that looked just like their mothers and sons that looked just like their fathers. Bridges earned his doctorate by figuring out that these exceptions had extra sex chromosomes. Using cytological observations of chromosome number confirmed by a series of mating experiments, Bridges demonstrated that sometimes chromosomes stuck together and an individual ended up XXX or XXY. This chromosomal non-disjunction meant that extra copies of the genes existed in individuals with extra sex chromosomes. Since two copies of a recessive gene allow it to be expressed, these individuals could appear just like their parent in terms of their traits and sex (Bridges 1916). Bridges' experiments combined the method of genetic crossing with microscopic observations of chromosomes and in doing so provided one of the foundational results that convinced other scientists that genes were in fact located on chromosomes (Brush 2002).

As the person chiefly responsible for tracking mutants in the fly room, Bridges took note of gynandromorphs as early as 1910 and spotted the first *Drosophila* intersex in 1920. All of the males in this initial brood were sterile, so they could not be subject to genetic experimentation. The females, however, could reproduce, and through cytological analysis, Bridges established that they had three sets of chromosomes instead of two. Through a series of mating experiments Bridges produced intersexes with three sets of autosomes and a variety of X and Y chromosome combinations. From these experiments, Bridges found that the extra autosomes seemed to make intersexuals appear more male. He could also produce what he called superfemales, which had three X chromosomes and two autosomes, as well as supermales, which had one X chromosome and two autosomes. These superfemales and supermales marked ends of a continuum of bodily differences. From the evidence of these experiments, Bridges proposed his genic balance theory where he claimed that bodily sex was determined by a balance between genes on sex chromosomes and autosomes. Bodily sex, then, was the result of the interaction of many different genes from different chromosomal locations (Bridges 1922; Richardson 2011).

Bridges' theory and Goldschmidt's theory had many similarities: both were based on experimental results, though in different systems, both proposed a balance between genetic factors located on sex chromosomes and autosomes, though Goldschmidt thought female factors were cytoplasmic, and both saw opposing sex factors at the genetic level producing a range of bodily sexes that formed a

continuum with intersexes as true intermediate forms. That said, Bridges' experimental system allowed him to confirm chromosome numbers easily using cytological observation. Goldschmidt's *Lymantria* system did not allow this kind of visual confirmation. Rather than abandon his *Lymantria* system, however, Goldschmidt rested his theorizing on the results of just his mating experiments. This meant that while geneticists using *Drosophila* could proceed to map sex genes to chromosomes and characterize them more precisely in terms of their transmission and location, Goldschmidt's experimental system could produce a wide range of intersexual forms, but without the same kind of gene identification, mapping, and characterization that was possible with *Drosophila*.

The most notable difference between Bridges and Goldschmidt lay in the extent to which they developed their balance theories. Bridges tied his theory directly to the measured differences in chromosome numbers. American genetics developed in an atmosphere that emphasized practical results, experimental progress, and a pragmatic style of research (Harwood 1993, pp. 49–50; Maienschein 1991, p. 259). Morgan had made an explicit decision to orient his group's work toward genes that consistently produced the same bodily or phenotypic effect. His group temporarily set aside problems of gene action, which required an understanding of the very complex processes of development. Goldschmidt's theory was based on consistent numbers of chromosomes with genes that had different strengths or valences. Drawing on his training in developmental biology, Goldschmidt championed a physiological approach that emphasized how a single gene could produce many different phenotypes depending on differences in development and environmental interactions. For Goldschmidt, the amount of enzyme or hormone that a gene produced, the rate at which it was produced, and when it was produced during development all contributed to a complex connection between gene and body that gave developmental processes the power to shape bodily variation from a singular genetic basis. Goldschmidt liked to point out this difference as he argued for his dynamic approach over the static approach of the *Drosophilists*, who though he made too much of this distinction (Goldschmidt 1950; Sturtevant 1965). In one of his last articles in 1938, Bridges acknowledged that both of their approaches had to integrate genes and development, but admitted that he saw bodily traits as the result of the interaction of many genes rather than the effects of single or small groups of genes mediated through physiological and developmental processes (Bridges 1939).

In Bridges' obituary for *Science* (1939), Morgan praised Bridges' many accomplishments, but when he turned to his work on sex determination, he treated it as an exceptionally theoretical line of research (Morgan 1939, 1940). In Morgan's words, "His work on sex determination was a brilliant venture into a more theoretical field, although here, too, it is important to observe that there was no idle flight of speculation but an adherence to actual evidence based upon his own thorough going observations" (Morgan 1939). This was a swipe at Goldschmidt, as well as an indication of the attitude toward what constituted "good genetics" in Morgan's fly room. Alfred Sturtevant, Bridges' co-worker in the Fly Room from the beginning, was less ameliorating when he judged Goldschmidt's balance theory to be quantitative, but without anything that was actually quantitatively measured (Sturtevant 1965, p. 85).

4 Balancing acts

Øjvind Winge was drawn into biology through natural history and a life long interest in mycology. He earned a doctorate in botany at Copenhagen University in 1910, and under the influence of Wilhelm Johannsen, who gave the field of genetics its name, he became interested in chromosome cytology. His first position in Denmark took him away from the plant world, however. As Johannes Schmidt's research assistant in the Carlsberg Laboratory in Copenhagen, Winge was introduced to fish genetics (Westergaard 1964). Schmidt had discovered sex-linked traits in guppies, *Lebistes reticulatus*, in 1920 (Schmidt 1920). Winge continued this line of research using color varieties to follow patterns of sex-linked inheritance (Winge 1927). Typically, in guppies males are colored and females are not. As Winge bred his fish, he occasionally found female fish with some of the color spots associated with males. Some of these females could be explained by an exchange of color genes from the Y chromosome to the X chromosome. This kind of exchange did not happen in experimental systems like *Drosophila*, and Thomas Hunt Morgan expressed his doubts about these results from Winge's fish (Morgan 1926).

Morgan's comments set off a bit of species politics with Winge responding in 1932 with the assertion, "I find it too dogmatic to assume that all organisms behave just as *Drosophila* do. In *Lebistes* you have more color genes in the Y than in any other chromosome, and you find crossing over between the X and Y" (Winge 1932, p. 344; Winge 1934; Hopwood 2011). For Winge, the idea of a genetic orthodoxy based on the lack of genetic exchange among X and Y chromosomes in *Drosophila* could not be reconciled with the guppy system or research he was also doing in other species, such as *Humulus* (hops) and *Melandrium*. The results pouring out of *Drosophila* genetics had granted that system considerable authority and would earn Morgan a Nobel Prize, but, for geneticists working in other systems, the idea of conforming to the *Drosophila* system denied other empirical realities and was laden with both unjustified species preference and even nationalism.

Like Aida, in 1930, Winge returned to the unusual female guppies showing male color patterns for further experimentation (Winge 1930). In order to determine the extent to which genetically female fish could be "masculinized," Winge found a variety (Maculatus) whose color pattern was always associated with the male sex. Winge hypothesized that the Maculatus color gene was tightly linked to a male determining gene on the Y chromosome. This meant that the chances that these two genes would be broken up during a chromosomal exchange would be small, so the Maculatus color pattern would act as a visible marker for the movement of the male determining gene. As Winge deployed his Maculatus males in new crosses, he got the normal pattern of males and females, but he also produced three females with other male color patterns. Because these fish did not have the Maculatus pattern, Winge inferred that they did not have a Y chromosome, and so were chromosomal females (XX) with male color genes. So what made these chromosomally female fish have male bodies? Winge postulated that these fish had other sex determining factors on other chromosomes and, in the varieties that he observed, the balance of these other chromosomes "tipped the balance" toward a male body. In effect, the

“sex chromosomes” (XX) had stopped being sex determiners. Instead, the autosomes with the strongest sex determining gene or genes had become the new sex chromosomes (Winge 1932). Winge’s interpretation followed Bridges’ genic balance theory of sex determination, but *Drosophila* could never do what guppies had done for Winge. With the *Lebistes* system, Winge could take the idea of a balance of sex factors and move it away from the *Drosophila* mindset where X and Y chromosomes were both distinct from each other and distinct from all other autosomal chromosomes.

When Winge read of Aida’s experiments with Medaka, the similarities were so great that he suggested in print that Medaka must be undergoing the same of kind of masculinization or sex reversal that he had observed in guppies, but not yet discussed in print. Aida did not respond immediately. Instead, he worked for 6 years with his Medaka system to determine whether non-disjunction or sex reversal explained the patterns he created in his mating experiments. Aida had produced a single white female in 1929. Spurred by Winge, he repeated his experiment producing another in 1931. To determine that these fish were chromosomally male (XY), Aida mated them to a red orange male. If both fish were XY, then there should be three times as many male as female offspring. He counted 55 females and 167 males, but worried that this was still not conclusive. So, he reasoned that half of these males should have two Y chromosomes, and would produce only males when mated with an XX female, which in exactly what his experiments revealed. Impressed by Winge’s case for fish, Aida concluded: “It is very interesting to see that in fishes which are well sex-differentiated like *Lebistes* and *Aplocheilus* one sex may change to the opposite one, and that YY male may be viable and fertile while it is lethal in *Drosophila*” (Aida 1936, p. 145).

Based on these experiments, Aida proposed a new interpretation of sex determination. Unlike Goldschmidt’s, Bridges’, and Winge’s interpretations that posited a balance of factors distributed across the sex chromosomes and the autosomes, Aida proposed that sex determining genes were found only on the autosomes and that the sex chromosomes held genes that functioned as “sexual exciters” that “stimulated” or activated the sex genes on the autosomes.¹ Sexual differentiation could then be explained in terms of the strength of sexual exciters on the sex chromosomes and quantity and strength of the autosomal sex determining genes, which set a specific threshold for sex expression. The sex reversed Medaka could then be explained in terms of a loss of potency of sexual exciters on the X chromosome that allowed only masculine genes to be activated in sufficient quantity to cross the expression threshold. So, even though the fish are XX, they appear to be male. Because Aida located his sex exciter genes on X chromosomes, it followed that female sex determination required more female exciters and male sex determination required fewer male exciters.

The loss of potency in sex determiners was imagined in terms of fluctuations of the amount of sex exciters, so that individuals in the same brood could show a

¹ By using anthropomorphic language of excitation, Aida’s understanding of sex chromosomes appears to be a case of what Sara Richardson calls “Sexing the X,” where human characteristics are ascribed to the X and Y chromosomes (Richardson 2011).

variable effect. This is not to say that a brood would have intersexual individuals. Aida thought that the sex excitors worked by a threshold effect creating either males or females. Indeed, for both Winge and Aida, their systems did not produce intersexes—only sex reversals, so they maintained a bodily dichotomy between male and female. Indeed, they extended this dichotomy to the genetic level with male and female genes, but allowed for genetic variability to arise through the balance of sexually distinct factors. Aida's threshold provides a binary filter for this variable balance of genetic factors that results in only male and female phenotypes. Like Goldschmidt, Aida was confident that his proposed theory could explain a wide range of cases and so constituted a general theory of sex determination. In his words: “the hypothesis of quantitative differences in the degree of sensitivity of the male and female sexual genes in autosomes and corresponding differences in the potencies of sex chromosomes in different sexes explains well many complex facts of sex differentiation, and I think that it is the general mode of sex differentiation” (Aida 1936).

Once Aida had constructed this interpretative framework, he used it to reinterpret Goldschmidt's results from *Lymantria* and Bridges' triploid intersexes in *Drosophila*. Although he says that his results in Medaka led him to question whether Goldschmidt's proposed male and female factors existed, he proposed that they could take the role of sex exciter genes that he postulated resided on the sex chromosomes. Assigning numerical strengths to these excitors and numerical thresholds, Aida carefully reconstructed seventeen different experimental crosses in *Lymantria* and demonstrated that his interpretation could explain the results of each. Interestingly, Aida does not question Goldschmidt's location of female factors in the cytoplasm, nor does he explain why *Lymantria* produce a range of intersexes and Medaka only produces sex reversal.

After Aida opened the issue of reinterpreting Goldschmidt's results, however, Winge offered his own reappraisal based on his own understanding generated through his guppy experiments (Winge 1937). As his biographer notes, “Winge always enjoyed a scientific argument, and whenever he entered a new field of genetics he almost invariably got into a fight” (Westergaard 1964, p. 363). Winge's system located all sex determiners on a mix of autosomes and sex chromosomes. What he found objectionable in Goldschmidt's interpretation was his insistence that female factors were not chromosomal, but were maternally inherited through the cytoplasm. This idea seemed to draw on earlier non-genetic explanations for the causes of sexual difference, and challenged the chromosomal theory of heredity created by Morgan and accepted by most geneticists. Using Goldschmidt's own quantitative system, Winge argued that Goldschmidt's own results could be explained by locating female factors on the sex chromosomes.

Goldschmidt also relished scientific arguments, and after his forced migration from Berlin to Berkeley, seemed to seek them out (Dietrich 2011). Even before he left Berlin, Goldschmidt had begun to shift his own experimental system from *Lymantria* to *Drosophila* as he ended his empirical studies on sex determination in favor of research on the gene, mutability, and homeotic mutations in *Drosophila* (Davis et al. 2009). Nevertheless, Goldschmidt was not shy about defending his past research or continuing to develop his interpretation of earlier experimental results.

In a 1937 paper, he answered both Winge and Aida (Goldschmidt 1937). As you might expect, Goldschmidt was not persuaded by either suggestion for alternatives to his interpretation based on his *Lymantria* experiments. Goldschmidt accused Winge of speculation—of inventing autosomal modifiers needed to tip the balance of sex factors instead of demonstrating their existence through experimentation. The same results, Goldschmidt argued, could be produced through his proposed mechanism of the physiology of gene expression and should have produced intersexes that Winge would have noted, if he had bothered to do any dissections on his fish (Goldschmidt 1937, p. 436). Goldschmidt was more approving of Aida's experiments, but saw his interpretation as a restatement of earlier ideas that had the same result as his own explanation for sex determination in terms of the potency or valence of sex factors located on the sex chromosomes. Because the two theories produced the same kind of calculations and predictions, Goldschmidt declared them to be the same “though couched in different language” (Goldschmidt 1937, p. 438).

During the Second World War, sex determination research, like much genetic and scientific research slowed or stopped. Goldschmidt and Winge moved on to other problems and other experimental systems. Aida left genetic research, and after the war worked for a Japanese maker of scientific models (Komai 1958). Bridges passed away in 1939. After the war, as other researchers on sex determination incorporated the results of these early experiments on sex reversal into their understanding of the biological diversity of sex determination, Winge and Goldschmidt both returned to the question of the genetic determination of sex (Crew 1933; Maienschein 1984; Ha 2011).²

In 1933, Winge was appointed Director of the Department of Physiology at the Carlsberg Laboratory in Copenhagen. Winge had always worked on a range of organisms, but after 1933, the Charter of the Carlsberg Laboratory required that its science be of some service to the brewing industry, so he turned his attention to yeast genetics (Westergaard 1964, p. 358). Over the next 23 years, Winge laid the foundations for this very influential experimental system by demonstrating sexual reproduction in yeast, and then showing that fermentation ability was inherited (Westergaard 1964, p. 363; Syzbalski 2001). But Winge had not left his guppies entirely. In 1947, he reported a series of experiments that he had done with E. Ditlevsen between 1935 and 1944, when the *Lebistes* stocks in the Carlsberg lab were discarded (Winge and Ditlevsen 1947). In this paper, Winge returns to Goldschmidt's criticisms from 1937 and focuses on the problem of explaining XX males. Although the letters themselves do not survive, Winge reports that he and Goldschmidt corresponded about their differing genetic interpretations of sex determination in 1935 (Winge and Ditlevsen 1947). According to Winge, Goldschmidt tried to persuade him that sex factors in the cytoplasm would explain the crosses producing XX males. Goldschmidt's formulation of sex determination predicted 50 % XX males from a back crossing experiment with XX males and a normal female. When Winge and Ditlevsen performed this cross in *Lebistes*, they

² Ha's “The Riddle of Sex” convincingly demonstrates the importance of hormonally based understandings of sex at this time. For present purposes, I have focused on a narrower set of genetic experiments and their interpretation.

only found one XX male among the offspring. This agreed with Winge's interpretation of sex determination based on multiple genes located on the autosomes and sex chromosomes, and not Goldschmidt's interpretation based on cytoplasmic factors. In Winge and Ditlevesen's words, "XX males appear when, through recombination including crossing-over, particularly strong male determining genes have accumulated in the autosomes" (Winge and Ditlevsen 1947, p. 82). Moreover, Winge and Ditlevesen argue that this interpretation agrees with results from experiments with the flowering plant *Melandrium* where strong male-determining genes on the Y chromosome and autosomes seem to play a central role in male sex determination.

The Second World War undoubtedly took its toll on scientific communication, and Winge and Ditlevsen did not take notice of Goldschmidt's own reconsideration of his reasoning in an article in *Science* from 1942. Before the War, Goldschmidt had moved into *Drosophila* research in his new position at the University of California, Berkeley. His experimental research focused on morphologically dramatic homeotic mutants, especially the podoptera mutant, that had legs instead of wings. The variability of these mutants fit well with Goldschmidt's ideas regarding the important role of development in modulating gene expression (Davis et al. 2009). In 1942, results from H. E. Warmke and A. F. Blakeslee on sex determination in *Melandrium* pulled him back again to sex determination (Goldschmidt 1942; Warmke and Blakeslee 1939). According to Goldschmidt, Warmke and Blakeslee's work focused his attention back on the Y chromosome. Before he had settled on the idea that female factors were cytoplasmic in the early 1930s, Goldschmidt had postulated that they were located on the Y chromosome. This was the position to which he returned in 1942. What motivated this reversal in positions was the recognition that his supposedly "crucial experiment" from the early 1930s may have overlooked a significant number of sterile males. Goldschmidt had thought he could detect all the XY males in his experiment, which, in retrospect, he realized that he could not. Already deeply engaged in *Drosophila* research, Goldschmidt did not have the *Lymantria* varieties to perform a "decisive experiment" to confirm his return to fully chromosomal sex determination. Nevertheless, he was willing to make this shift based on "Blakeslee's work" (Goldschmidt 1942, p. 121). Nowhere in this short note to *Science* does Goldschmidt mention Winge, although Goldschmidt's new position was certainly amenable to that being advocated by Winge. Perhaps *Melandrium* allowed Goldschmidt to accept Winge's arguments indirectly, providing a "neutral" experimental system.

5 Conclusion

Experimentation is a hallmark of twentieth-century biology, and genetics is a quintessentially twentieth century science. Understanding the genetic foundations of sex depended on the creation of experimental systems that would allow researchers to generate and mark differences across generations. These generations of marks constituted the genetic reality of sex and revealed it to be a multidimensional

scientific object that required distinctions between genetic, chromosomal, and bodily sex.

Richard Goldschmidt, Calvin Bridges, Tatsuo Aida, and Øjvind Winge each developed different experimental systems designed to produce hereditary understanding of sex (see Table 1). However, even the categories and phenomena of bodily sex differed across these systems. Aida's and Winge's fish had dimorphic males and female bodies, while Goldschmidt's and Bridges's insects exhibited ranges with distinct male and female sexes and intermediate gradations of intersexes. This "pronounced difference," to borrow Winge's phrase, did not inhibit these researchers from comparing and generalizing across their four systems (Winge and Divtlevsen 1947).

Because experimental systems mediate how researchers interact with the world, each of the systems discussed here became a lens for how each researcher interpreted their own results as well as each other's results and theories. While each of the four biologists advocated a balance theory of sex determination, their theories had different features that reflected what they understood to be the reality of how

Table 1 Four approaches to the genetics of sex determination and sex reversal

Researcher	Richard Goldschmidt	Calvin Bridges	Tatsuo Aida	Øjvind Winge
Experimental species	<i>Lymantria dispar</i>	<i>Drosophila melanogaster</i>	<i>Aplocheilus latipes</i>	<i>Lebistes</i>
Organismal class	Insect	Insect	Fish	Fish
Sex categories	Gradation from Male to Female. Regular experimental production of intersexes	Gradation from super male to super female. Regular experimental production of intersexes	Male or Female No intersexes	Male or female. Intersexes acknowledged but very rarely produced
Theory of Sex determination	Balance of male and female determining genes on sex chromosomes and autosomes. From 1934 to 1942, female genes were considered to be cytoplasmic and so maternally inherited	Balance of male and female determining genes on sex chromosomes and autosomes	Balance of male and female sex exciter gene genes on sex chromosomes and a balance of male and female sex genes on autosomes that set a threshold for expression	Balance of male and female determining genes on sex chromosomes and autosomes
Role of sex chromosomes	The strongest sex determining genes are on the sex chromosomes	The strongest sex determining genes are on the sex chromosomes	Exciter genes are on the sex chromosomes and act on sex determiner genes on autosomes	Strong sex determining genes can be found on sex chromosomes or autosomes

they experimentally produced sex. Winge could breed his guppies to make autosomes into the primary sex determining chromosomes, which Bridges and Goldschmidt could not. As a result, he placed more emphasis on determining genes as opposed to determining chromosomes. Goldschmidt's complex history of experimentation led him to advocate cytoplasmic heredity for female factors throughout the 1930s, even when no one else agreed.

All of the geneticists considered here decided to place the results generated from their particular experimental system into a theoretical or interpretative framework, and to compare the strengths and weaknesses of these theories. While these theories and criticisms traveled globally, the experimental systems of each researcher were not as easily exchanged. That said, Goldschmidt switched from *Lymantria* to *Drosophila* as he migrated from Germany to the United States, and Winge had multiple genetic systems under investigation. Nevertheless, the differences in the kinds of results each system could produce had a strong pull. Winge expressed his organismic loyalty in his opposition to the universalization of *Drosophila* results. Aida offered systematic reinterpretation of Goldschmidt's decades of *Lymantria* experiments in order to bring them in line with his own experimental results in Medaka. These conflicts over how best to formulate a balance theory of sex determination and the subsequent rounds of mutual reinterpretation were certainly influenced by personal history, differences in style and training, as well as differing ideas about sex, genes, and gene action. But, by comparing how four different experimental systems were brought to bear on the same genetic problem, we can also claim that the interpretive differences between Aida, Bridges, Goldschmidt, and Winge were rooted in differences within their experimental systems that each constituted sex and sex determination in substantially different ways.

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