Perspectives

Anecdotal, Historical And Critical Commentaries on Genetics

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Emil Heitz (1892–1965): Chloroplasts, Heterochromatin, and Polytene Chromosomes

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TANGLED nuclear threads: EMIL HEITZ is frequently said to have discovered, together with HANS BAUER, polytene chromosomes in Diptera. What is incorrect in this statement is the word "discovered." Priority for this should go to BALBIANI (1881). But at that time the phenomenon was understood as a tangled continuous thread, called *spireme* (TÄNZER 1922; KAUFMANN 1931). An early suspicion that the oversized structure might consist of individual chromosomes was coupled to the idea of a constant number of elements (RAMBOUSEK 1912; for review, BEERMANN 1962). This postulate could not be tested as long as tissues containing giant nuclei were cut into microslices. The difficulty was overcome when the technique of tissue squashing was applied by a botanist at Hamburg University. Heterochromatin could now be studied as a general property of chromosomes.

It is fitting to discuss the history of ideas about heterochromatin at the present time. There has been a recent resurgence of interest in heterochromatin, as molecular methods provide a way to study the subject at a deeper level. This is also evidenced by several recent articles in GENETICS, including one by LE *et al.* in this issue.

The Heitz method: Avoiding the time-consuming use of a microtome, HEITZ (1926, 1928a,b, 1933a) fixed plant material in two parts of alcohol and one part of acetic acid. He then stained it in carmine acetic acid (45%) and prepared, with needles, a single cell layer. STEVENS (1908) and BELLING (1926) had introduced similar methods. However, to obtain the best metaphase spreads free of cytoplasm, HEITZ applied gentle pressure to the cover slip. Thus, the specimen was attached to the slide and was prevented from being carried off when the slide was thoroughly boiled. Later, the more delicate Dipteran tissues were not boiled but cautiously heated. "The described preparation can be done within a moment after some practice. Within half an hour, 4-6 specimens can be produced" (HEITZ 1933b, p. 726; 1936). This technique, nicknamed *hei(t)zen* (heating), was adopted first at the Kaiser-Wilhelm Institute in Berlin-Dahlem (STERN 1931; GEITLER 1962; G. MELCHERS, personal communication) and at Würzburg University (HAUPT 1932; J. GREHN, personal communication).

The longitudinal differentiation of mitotic chromosomes became apparent, and the terms euchromatin and heterochromatin were coined (HEITZ 1928b). Chromatin is the substance that transforms into chromosomes during mitosis (BOVERI 1904). According to this view, euchromatin is chromatin proper, the chromosomes that are structurally altered during telophase so that their individuality is not recognized in the nucleus. Heterochromatin behaves differently from euchromatin in morphogenesis; specific (parts of) chromosomes do not participate in telophase reorganization (HEITZ 1935).

Heterochromatin in Bryophyta: Using the liverwort *Pellia epiphylla* (*Jungermaniidae*) and exploiting prophases, metaphases and telophases as well as interphase nuclei, HEITZ found evidence that identical chromosome sections are constantly heterochromatic (heteropycnotic). Heterochromatin was found without exception in all genera of acrogynic liverworts (HEITZ 1928b, p. 796), whereas in anacrogynic species the heterochromatin of autosomes depends on the presence of a heteropycnotic *minute* chromosome (p. 801). "With 70 species of true mosses from 20 families, always one chromosome behaves differently. It does not disappear in telophases as do the other chromosomes" (p. 815). HEITZ provided evidence that heteropycnosis is not an artifact. "Initially, it was expected that it must also be observed in vivo, at least in resting nuclei (in interphase). Nuclei of fully grown cells lying at the outer cell wall and not greatly obscured by chloroplasts show the heterochromatin very well" (p. 790). "The cause of heteropycnosis can only lie in the concerned chromosomes themselves" (p. 815).

"It may arouse amazement that the outlined facts were up to now overlooked. However, without the boiling method I would not have visualized the regularity of the phenomenon so soon. The advantage of my method, apart from saving time, is that only chromatin becomes intensely stained, whereas plasma and above

all the nucleoli scarcely take color. Thus, one need not search for the right degree of differentiation, since any properly prepared specimen is, by itself, correctly *differentiated*" (p. 802). Boiling in aceto-carmine had produced the first C-banding patterns (PASSARGE 1979).

Heterochromatin "in plants and in substantial details also in animals was hitherto an unknown phenomenon" (HEITZ 1928b). Therefore, he started a series of cytological investigations searching for heteropycnosis in somatic cell nuclei of Diptera.

Heterochromatin in Drosophila: *The Physical Basis of Heredity* by THOMAS HUNT MORGAN (1919) became well known in Germany through an authorized translation by HANS NACHTSHEIM (MORGAN 1921). The book and contact with the "genetics community" (HARWOOD 1993) stimulated EMIL HEITZ (1933b) to breed at least five Drosophila species in the greenhouse. *Drosophila funebris* was caught in the Botanical Institute Hamburg. The species was easily recognized, from the chromosomes. *D. melanogaster* was received from CURT STERN, Kaiser Wilhelm Institute for Biology in Berlin-Dahlem. *D. simulans* was from the Institute for Experimental Biology in Moscow, mailed by Fräulein Dr. FROLOWA (1925). *D. hydei* and *D. virilis*, "originally from the United States," were from RUDOLF GEIGY, Zoological Institution at Basel.

The first attempt was made with the MORGAN fly. HEITZ (1930) was surprised that cells from different organs of larvae and adults gave pictures similar to those known in true mosses. He saw one and sometimes two vacuolated and intensely stained blobs of chromatin during interphase.

Since *D. melanogaster* appeared "rather unfavorable with respect to cytology," HEITZ (1933b) continued with *D. funebris*. Its karyotype was known to contain two remarkably large chromosomes of similar length in both sexes (METZ 1916, 1926). However, while one of these chromosomes (the *Y*) was totally heteropycnotic, the other was differentiated into a euchromatic half and a proximal heterochromatic section. With the finding of partial heteropycnosis in the *X*, a new "structural type" of sex chromosome was detected. This was in contrast to the known "quantitative type" where *X* and *Y* are of different sizes.

After these preliminary examinations, HEITZ (1934a) returned to *D. melanogaster* and added *D. virilis*. The sex chromosomes of these species likewise were of the structural type just described for *D. funebris*. Furthermore, partial heteropycnosis characterized the autosomes. The fact that heterochromatin is proximally localized in any autosome was termed "equilocal heterochromacy." Figure 1 summarizes the findings on heterochromatin distribution in somatic nuclei of the three Drosophila species.

Introductory remarks (HEITZ 1933b) described the main research impetus. (i) Chromosomes are the material substratum of genes. (ii) The genes are linearly arranged according to MORGAN's conclusions from transmission genetics. Now, for the first time, the new technique demonstrated a longitudinal differentiation in cytological entities, euchromatin and heterochromatin. Heteropycnosis characterized not only sex chromosomes (SHOWALTER 1928) but likewise autosomes. Furthermore, heterochromatin was a phenomenon of general biology occurring in both animals and plants. Therefore, Professor WINKLER (who had coined the term *genome* in 1920) "generously put at my disposal the resources of the Botanical Institute for these studies."

HEITZ (1929, 1932) had imagined that "euchromatin is genicly active, heterochromatin genicly passive. Heterochromatic chromosomes or pieces of chromosomes contain no genes or somehow passive genes." However, the results from MORGAN's laboratory (MORGAN *et al.* 1925; MULLER and STONE 1930; MULLER and PAINTER 1932) forced a revision: "My ideas are not correct, because genes which lie within the heterochromatin do intervene in the developmental process of an organism. Nevertheless, the density of genes in a chromosome is related to the longitudinal differentiation in euchromatin and heterochromatin. Euchromatic pieces are rich, whereas heterochromatic ones are at least poor in genes. One has to suppose further that the genes are evenly and linearly distributed within the euchromatin" (HEITZ 1934a, p. 266). Interestingly, he discussed whether the Drosophila genes *light* and *rolled* are within the euchromatic or heterochromatic environment (p. 264).

Polytene chromosomes: HEITZ was promoted from *Privatdozent* to extraordinary professor in July, 1932. At that time, BAUER worked as a postdoctoral fellow and scientific volunteer in the Institute for Marine and Tropical Diseases at Hamburg. There he became acquainted with the Feulgen procedure as being specific for the chromosomal substance (BAUER 1932). HEITZ (1931) also was aware of this, but he preferred boiling in carmine acetic acid because he could not discriminate heterochromatin and euchromatin with the Feulgen technique (HEITZ 1935, p. 409). A joint venture had been started with a very convenient subject contributed by HERMANN WEBER (1933), a recognized entomologist at Danzig. The results from the black "hairy garden midge" were considered so important that the manuscript was submitted on July 31, 1932. Thus, "Evidence for the chromosomal nature of nuclear loops in the tangled nuclei of *Bibio hortulanus* L." (HEITZ and BAUER 1933) appeared ahead of the Drosophila papers.

The authors had followed their standard procedure of chromosome analysis: first of all, one has to investigate mitotic prophases and metaphases, after which polytene structures can be analyzed. Somatic mitoses were obtained from neuroblasts and follicular epithelium of ovaries. Prophases in *B. hortulanus* showed five pairs of chromosomes that separated into 10 metacentric elements in metaphase (p. 69).

Tangled nuclei were found in salivary glands, midgut,

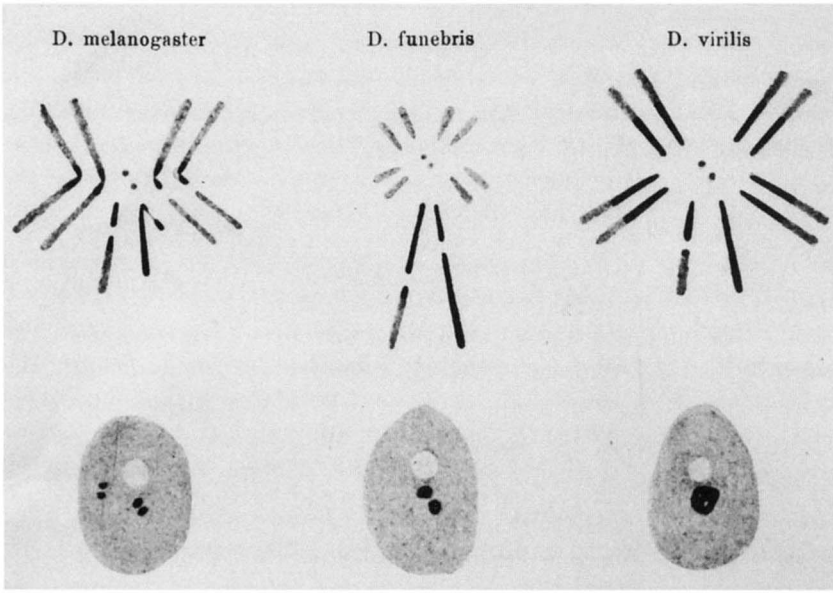

FIGURE 1.—Schematic summary of chromatin structures from three Drosophila species. Longitudinal differentiation in euchromatin and proximal heterochromatin is evident in metaphase configuration. The heteropycnotic material is associated with one or two chromocenters in interphase nuclei (HEITZ 1934a, Figure 9; 1935, Figure 7).

Malpighi tubes, and occasionally in the brain. Especially from the Malpighi tubes it became clear that the large nuclei did not contain a continuous thread. There were always five clearly separated thread sections, each double and different in length. Furthermore, structural features (nucleolus and terminal peculiarities) were not randomly distributed but were found characterizing the individual nuclear loops. Last but not least, they were Feulgen-positive. The results led to the conclusion that the giant threads are twin chromosomes in haploid number (p. 72). The synapsis of homologous chromosomes was later employed extensively as a simple way to detect heterozygous chromosome rearrangements (PAINTER and STONE 1935).

Contest for priority: "The most striking recent development in cytology is the discovery of the chromosomal nature of the long known giant structures in the nuclei of the salivary glands of Diptera. This discovery, made with Bibio (Heitz and Bauer 1933), was extended to Drosophila by Painter in 1934" (STURTEVANT AND BEADLE 1939, p. 364). In Hamburg, both authors were aware of their achievement. "Heitz and Bauer (1933) have provided the final evidence with *Bibio hortulanus* and thus for Diptera generally that there exist enormously enlarged chromosomes" (HEITZ 1933b, p. 727).

No earlier than December, *Science* published a provocative statement by THEOPHILUS SHICKEL PAINTER (1933b) on polytene chromosomes in *D. melanogaster*: "It has long been known that in the functioning salivary glands of many dipteran larvae the chromosomes show an elongated and annulated structure." HEITZ immediately and harshly commented, "Almost one year after the publication of our investigations with *Bibio hortulanus* and shortly after the appearance of the said work (on *D. melanogaster*), Painter reports preliminarily (not less than three times, December 1933, 1933, 1934) and in greater detail (1934, here giving reference to our work) on a 'new method' for the qualitative analysis of *Drosophila melanogaster* chromosomes. Painter's statement 'It has long been known . . .' was not correct at all. Evidence for the chromosomal nature of nuclear loops was demonstrated initially by our work. Clear objections must be raised to the mode of Painter's account" (HEITZ 1934b, p. 588; see also PAINTER 1933a, 1934b,c, 1935).

It is noteworthy that the "greater details" had already been submitted to GENETICS in May, 1933, but unfortunately appeared one year later (PAINTER 1934a).

The objections obviously were taken into account, and the rephrased sentence reads, "All cytologists have known for a long time that in the salivary glands and other tissues of the larvae of Diptera in general there occurs what has been called a 'permanent spireme.' In the nuclei of such tissues structures called chromosomes are very large and show very conspicuous bands" (PAINTER 1934c). Troubles came not only from PAINTER but also from the young co-author. HEITZ (1933b, p. 723) complained in a footnote, "Bauer (1933) has just reported on partial heteropycnosis in the oocyte nuclei of *Dytiscus marginatus*. My assessments on partial heteropycnosis in *Drosophila funebris, D. melanogaster* and *Scatophila unicornis* were made earlier than those of Bauer with Dytiscus which is not quite obvious from his account."

A burst of research in the new field of cytogenetics had been initiated (HEITZ 1935, p. 429). LOTHAR GEITLER (1934) reported on polytene chromosomes in Simulium, KING and BEAMS (1933, 1934) dealt with Chironomus, and METZ and GAY (1934a,b) with Sciara. KLAUS PÄTAU (1935) focussed on *D. simulans*, and C. C. TAN (1935) did so on *D. pseudoobscura*. THEODOSIUS DOBZHANSKY (1935) recognized that *D. miranda* was different from the sibling species *D. pseudoobscura*, as shown by the banding in polytene elements.

Natural banding pattern: The constant structural characters of polytene chromosomes were already apparent in the first approaches. Especially the discontinuously banded pattern of the giant nuclear loops was recognized, proving the individuality of the chromosome pairs. "The loci of these chromomere-like disks are not randomly distributed but constant. This constitutes new evidence that chromosomes possess a constant differentiation in the direction of their longitudinal axis" (HEITZ and BAUER 1933, pp. 78, 81).

The constancy of polytene bands was also detailed in a following paper (HEITZ 1934b), and the transatlantic success was acknowledged: "The usefulness of giant chromosomes of Diptera for localizing exactly the (Mendelian) factors was shown for the first time by Painter (1933, 1934), who had collected rich material for investigation" (HEITZ 1935, p. 433). Further, "One has to emphasize the work of Bridges (1935), who has carried forward the analysis of longitudinal differentiation in this species (*D. melanogaster*) so far that it is difficult to beat. Furthermore, Bridges has established a very useful system of assignment" (p. 430).

Multistranded elements: The size of the novel chromosomes was initially described as "magnified" and "giant" while the term "polytenic" was introduced by KOLTZOFF (1934). GÜNTHER HERTWIG (1935) noted that the gigantic dimensions are achieved by real growth, *i.e.,* by multiple doubling of the genome: "Thus, any gene is present in the salivary gland chromosomes of *D. melanogaster* at least 256-fold or 512-fold, and not only 8 times as Koltzoff (1934) and Bridges (1935) recently thought. . . . A substantial point in the discovery of Heitz is that not the number, but only the size of the chromosomes is increased in the salivary gland nuclei. These giant chromosomes lie in enormously enlarged nuclei."

Also HEITZ (1935, p. 430) refers to these papers: "Bridges (1935) and Koltzoff (1934) independently have explained the giant size of these chromosomes this way: There is not a single and strongly enlarged chromonema. The thickness is brought about when the multiplied chromonemata remain in mutual connection between each other." (Nowadays we prefer the word chromatid instead of chromonema.)

An explanation of the extraordinary size must connect the giant structure with the "normal" chromosome. In this view, BAUER (1937, p. 72) has summarized, "Thus, the giant chromosome is a bundle of identically built fibrils of which the homologous parts are at the same level."

Heterochromatin under-represented: Because *D. virilis* possesses some 50% mitotic heterochromatin, it was assessed as especially suitable for investigating chromosome development in the soma. "While euchromatic sections of the chromosomes increase to gigantic size during the growth of the nuclei, the heterochromatic sections, united in a collective chromocenter, are not able to do this . . . The heterochromatin proper is named α-heterochromatin from now on. The adjacent heterochromatin, like the former, does not reveal any differentiation in chromomeres, but has the capability of growing in common with the euchromatin. This β-heterochromatin, as it might be called from now on, possesses only a minor extension and cannot be recognized as such in somatic prophases, while the α-heterochromatin makes up half of the rod-shaped chromosomes" (HEITZ 1934b, p. 596).

Contemporaneous researchers had explained that chromosomal growth is caused by chromatid multiplication. Thus, the original definition of α-type heterochromatin corresponded to suspension from endoreplication rather than to condensation. However, PAINTER (1933b, p. 586) had discussed alternative mechanisms: "Either the inert material of both the X and Y has been eliminated during ontogeny (of *D. melanogaster*), by diminution or some similar process, or this material exists in the salivary nuclei in some unrecognized form not visibly connected with the chromosomes." The idea of elimination probably goes back to Würzburg where PAINTER had spent several months in 1913–14 with THEODOR BOVERI (WAGNER 1970; BOVERI 1910). But HEITZ (1935, p. 433) remained persistent: "The heterochromatin of the Drosophila species is also present at the giant chromosomes. Painter, who believed earlier (1934) that the inert region would be eliminated in the loop-containing nuclei, as he could not find an equivalent, has recently (1935) joined my opinion."

The HEITZ hypothesis of under-replication in larger somatic nuclei was also attacked by BAUER (1936, p. 217), then a research fellow at the California Institute of Technology in Pasadena: "Observations in Chironomidae led me to the conclusion that heterochromatic regions of salivary gland chromosomes are composed of the same number of chromonemata as the euchromatic strands, the difference between them being due to the structure of the single chromomeres." Regarding *D. pseudoobscura,* Figure 5 in his paper is a diagram presenting the two types of chromomeres without local under-representation of chromatids.

HEITZ dismissed: Looking back, shortly after his seventieth birthday, HEITZ wrote to CURT KOSSWIG, then Dean of the Faculty of Mathematics and Sciences, "It is for me a special honor to be made an honorary doctor by the Faculty of the University of Hamburg because I actually have made my most essential works at the Institute for General Botany there." He had joined the staff in November, 1926.

However, on February 4, 1937, EDGAR IRMSCHER, the curator at the Institute for General Botany and thus a close colleague of HEITZ, wrote an official letter to the Rector of the Hamburg University. IRMSCHER did so as the *Gaudozentenführer* of the National Socialistic German Labor Party. He reported to the Rector, Prof. ADOLF REIN, "that Prof. Heitz who, under the law, has to be

regarded as non-Aryan, will give a lecture on heredity." The Nazi official recommended cancellation of this lecture, otherwise certain circles might make trouble for the University (ROLAND HEITZ, personal communication; Hamburg Staatsarchiv 1937). The Rector immediately conferred with HANS WINKLER, director of that institute. Because of this intervention, HEITZ changed his lecture title to "General Genetics" for the rector's files, although the former title "Introduction to Heredity" had already been printed in the lecture timetable (Hansische Universität 1936).

More serious consequences arose from the notice that HEITZ was not pure Aryan. His maternal grandfather, Dr. MORITZ SCHWALB (1833–1916), had been Jewish and a protestant clergyman. From 1867 to 1894, he served as an elected parish priest in Bremen and became known for his critical and liberal sermons (SCHWALB 1884; HUNTEMANN 1969).

The German Public Servant Law had just been amended on January 26, 1937. According to §25, an official as well as the spouse had to be of German or related blood. Thus, even partially Jewish descendants were not allowed to teach at German universities (BRAND 1937). A cascade of documents, produced by the university and the government, culminated in a claim for the dismissal of HEITZ as nonpermanent extraordinary professor (Figure 2). However, the academic grade *Doctor habilitatus* expressly remained untouched.

A letter written by HEITZ pointed out that he was $^3/_4$ Aryan. His paternal grandfather, also named EMIL HEITZ (1885), had been rector of Strassbourg University. His father was a recognized German publisher (PAUL HEITZ 1902). The family had owned the Strassbourg University Press for generations (BURGUN and RAY 1984). His own service as a volunteer and sergeant with the German artillery during World War I was also mentioned. As in many similar cases, the Minister for Science, Teaching, and National Education made a final decision in Berlin. According to §18 of the Imperial Habilitation Rule (Reichs-Habilitations-Ordnung of December 13, 1934), HEITZ was to be removed from the register of professors by August 17, 1937. His last salary was to be paid in October of that year.

This was a shock to a family with four children, ROLAND (then 12 years old), THOMAS (10), ELISABETH (9) and SEBASTIAN (4). Probably Mrs. ELISABETH HEITZ (née STAEHELIN) took the initiative to move to her Swiss native town Basel where her mother MARTHA STAEHELIN-LINDER bought a house for the refugees.

Fate and science: JOHANN HEINRICH *EMIL* HEITZ was his full name. He was born in Strassbourg on October 29, 1892. In the fall of 1912 he went to Munich where he attended 22 lectures on hereditary science by RICHARD GOLDSCHMIDT (1913). Two semesters (1913/1914) were spent at Strassbourg University. World War I (1914–1918) interrupted his course of studies.

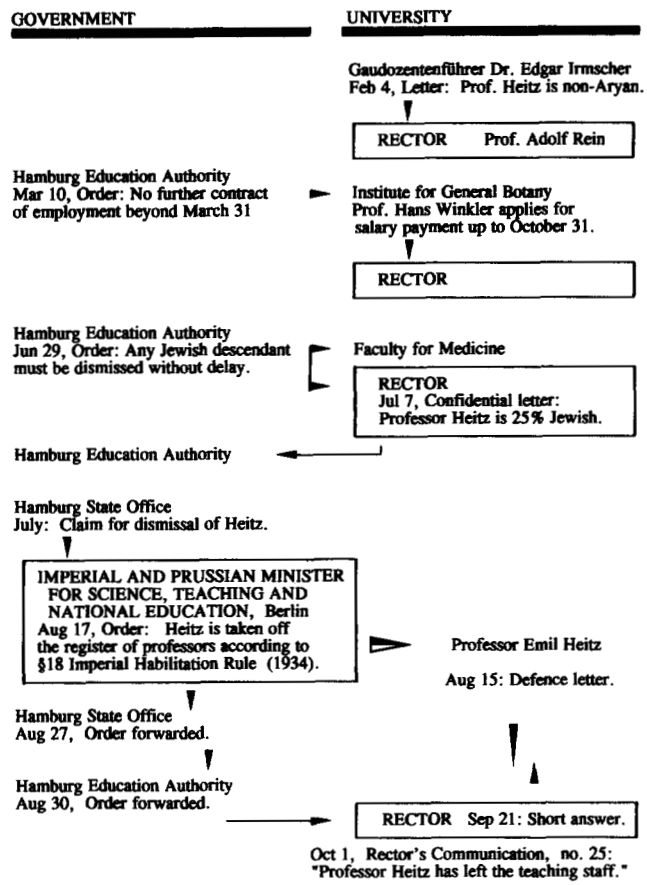

FIGURE 2.—Dismissal of HEITZ from Hamburg University during 1937 (Hamburg Staatsarchiv, Hochschulwesen 1937).

After the war, he met ELISABETH STAEHELIN (1896–1979) when both were students of biology at Basel University. HEITZ moved to Heidelberg and became a Ph.D. student of the plant physiologist LUDWIG JOST. Final examinations were held June 7, 1921, and his thesis on division of chloroplasts came out the following year (HEITZ 1922). He spent nine months as a postdoctoral fellow at Tübingen; during this time ELISABETH and EMIL married. From June, 1922 to May, 1924, HEITZ was scientific assistant to FRIEDRICH BOAS, Institute for Fermentation Physiology at Weihenstephan, Bavaria. A further interval (June, 1924 to September, 1926) was spent at the Prussian University at Greifswald. There, he not only did the job of a botanist but also took advantage of a working place at the Zoological Institute with PAUL BUCHNER.

Giving his inaugural lecture on the problem of speciation on November 3, 1926, HEITZ made a splendid start in Hamburg. "It was here that he spent the most fruitful 11 years of his scientific life" (FLÁVIO RESENDE 1962).

At Basel University, he was also made an extraordinary professor for Botany. RESENDE visited him in 1938 and "found out that his salary was less than that of a tram conductor of that city. The situation improved later, but was never very good." LEWIS J. STADLER in-

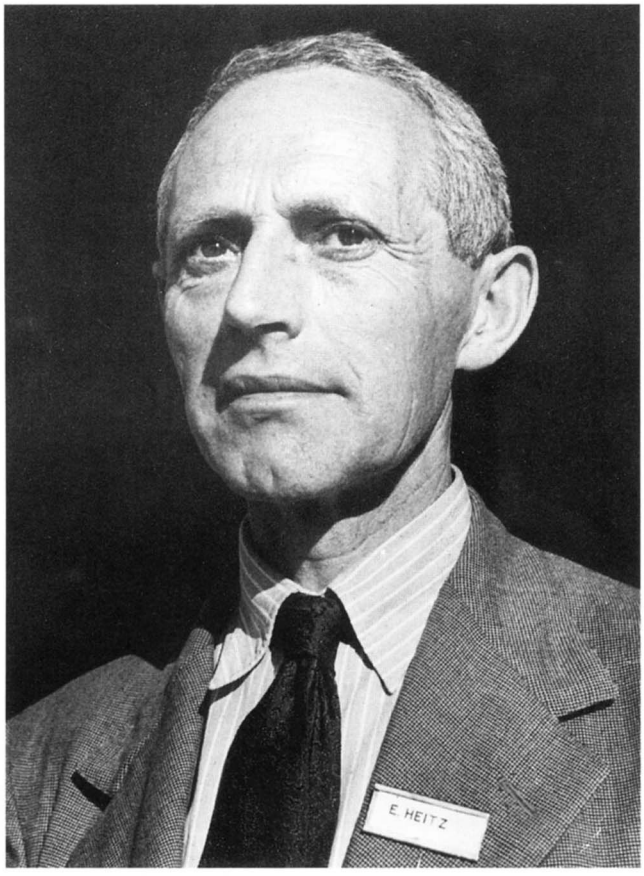

FIGURE 3.—EMIL HEITZ (age 56) at the Eighth International Congress of Genetics, July 7–14, 1948, in Stockholm (BONNIER and LARSSON 1949). Portrait by ESKO SUOMALAINEN (Helsinki).

vited HEITZ to join the University of Missouri, and the family prepared for the move (ROLAND HEITZ, personal communication). The passage was prevented when Germany declared war against the United States on December 11, 1941. Later, in 1947, HEITZ received Swiss nationality and was visiting professor at the University of Missouri from February to June (HEITZ 1955). "However, he did not like the American way of life. Even Hamburg was strange to him. He wrote me a letter from Missouri full of nostalgia that made me quite sad. He returned to Basel" (RESENDE 1962).

These unhappy circumstances changed in 1948 in consequence of the Eighth International Congress of Genetics (Figure 3). There, in Stockholm, EEVA THERMAN learned of the bad situation and informed GEORG MELCHERS (personal communication). The latter provided a laboratory in his department at the Max Planck Institute for Biology and HEITZ became visiting professor at Tübingen University in 1952. On April 1, 1955, EMIL HEITZ became a scientific fellow of the Max Planck Society. This was a final realization of a plan of FRIEDRICH WETTSTEIN (1895–1945), who in 1937 had intended for HEITZ to be in the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem (MELCHERS 1987; HENNING and KAZEMI 1993). After August 30, 1955, HEITZ was honorary professor of cytology at Tübingen. He did not return to active chromosome research but followed his interest in the ultrastructure of chloroplasts (HEITZ 1960). He retired on October 31, 1961, moved with his wife to Basel, and spent some time in his summer house, *Casa rossa*. In 1962, he received honorary doctorates from the universities of Berlin, Cologne and Hamburg.

EMIL HEITZ died at Lugano, Switzerland, on July 8, 1965, as a result of a broken thigh bone, and was buried in Basel.

Encouragement and information were given by WOLFGANG O. ABEL (Hamburg), HILDE ATZLER (Tübingen), FRANZ BRABEC (Hamburg), HEINRICH EITZEN (Kiel), JOSEF GREHN (Wetzlar), ELISABETH GÜNTHER (Greifswald), ELISABETH HAUSCHTECK-JUNGEN (Zürich), ROLAND HEITZ (Zürich), MARION KAZEMI (Berlin), ROLAND MALY (Kriens), GEORG MELCHERS (Tübingen), CLAUS PELLING (Tübingen), GÜNTER REUTER (Halle), ARMIN SPILLER (Berlin), DAVID STADLER (Seattle), the late ESKO SUOMALAINEN (Helsinki), VIT TASEVSKI (Sydney), RAYLA G. TEMIN (Madison), EEVA THERMAN (Madison), RENATE ULLMANN née DÖRMER (Tübingen), and STEFAN WULF (Hamburg).

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