Theodor Boveri

Fritz Baltzer

Theodor Boveri was born in Bamberg in 1862, the second of four sons of a physician. He lived to be only 53 years old, yet despite his early death he left behind a great and complete accomplishment. Although half a century has gone by since then, for the most part his work remains valid. If a great part of it has now become anonymous, only loosely connected with Boveri's name, it is all the more a fitting task to resurrect at his 100th birthday the personality and some important results of the work produced by this pioneer.

The question often arises as to how the Boveris, a Frankish family living in Bamberg, came by their Italian name. A Carolus Boveri migrated around 1590 from Savoy to Franconia; in the course of time the kindred developed into a purely Frankish stock. Even the phenotype changed from Italian to Frankish. Boveri himself used to say jokingly that people were always disappointed on seeing him for the first time. From his name they always expected something interesting and swarthy (*1*). And that was not at all the case with this man (Fig. 1): he had dark blond hair and very penetrating grey-blue eyes.

Boveri's works stand, like milestones, each one an individual, rounded unit, with basic facts and at the same time with the wisdom that only a master can offer. Not a few of his works are voluminous tomes in a way that is quite unmodern, and yet despite their length they are written in a concentrated, plastic style. Regarded from this angle, Boveri represented classicism through and through. He customarily said that writing was a torture for him, but nevertheless he treated it also as an art. Looking at his illustrations—for example in the *Ascaris* work of 1899, which he dedicated to his teacher, the anatomist C. v. Kupffer—one can be swept away with admiration for the simultaneously artistic and true-to-nature forms. It thus becomes understandable that this investigator, who from his youth on sketched, painted, and played musical instruments, wanted as a young man to become a painter.

Along with his major works, and often many years in advance of them, one finds along Boveri's scientific path a number of short communications. Studying these, one recognizes that the roots of Boveri's whole achievement are to be found during the time he spent in Munich between his 25th and 30th years. Working with tremendous energy, the most critical intelligence, and rapidity of perception, he discovered a wealth of significant facts in the short period between 1885 and 1890 and was led by them to important new theoretical knowledge. Impressive examples of this are his observations on multipolar mitoses (1887) and on the diminution of the chromosomes in *Ascaris* (1888). The multipolar divisions led him 12 years later to the theory of inequality of the chromosomes, the diminution to the problem of nuclear differentiation during embryonic development. He had the patience to wait, to let the material and also his thoughts grow.

Early Work

Boveri did not begin his scientific work in the field in which he achieved his great successes. He worked in the anatomy department at Munich on histology, studying the structure of nerve fibers, and obtained his Ph.D. on this subject in 1885 from the philosophical faculty of the same university. He may have gone into anatomy because his family's situation was insecure and he could thus keep his way open for a medical career. Von Kupffer, the Munich professor of anatomy, remained a fatherly friend to him.

In addition, if one may express it this way, the department of anatomy made him the gift of a lifelong friendship with August Pauly, a zoologist 12 years older than he, well endowed from an artistic standpoint. Pauly's chief work had to do with a Lamarckian theory of evolution.

Pauly was probably the first to recognize Boveri's importance. In his diary is to be found the following charming and at the same time prophetic judgment regarding Boveri's doctor's dissertation: "I expected a dry, histological piece of work and found something of great excellence. Every word and every part of the paper is fully thought out, thoroughly intelligent and mature. And all this as the result of talent. Seldom does so good a paper appear from the pen of so young a man. It shows an unusually keen microscopic eye and an equally clear intellectual sense for the matter under observation." How deeply anchored in Boveri this friendship was can be seen in part of a 1905 letter, dating from the period in which he worked on his rectoral address entitled "Organisms as historical beings," in which he examined critically Pauly's psycho–Lamarckianism. "Now I find myself daily remembering that spring 20 years ago, when we sat next to each other in the anatomy lab and became friends. Since this occasion is a sort of jubilee, let me express for once how much happiness and precious memories I gained from this friendship, and I still continue to draw on it."

Friendships generally played an important role in Boveri's life, and since he was a very good, lively correspondent, a multitude of letters to his friends, and also to his younger brother Walter and the latter's wife, give a captivating picture of his personality and of his time.

At Würzburg, W. C. Röntgen, his colleague in the physics department, became an intimate of Boveri's. In this case, too, a passage in a letter reveals how important personal bonds were for Boveri. "We agree completely," he wrote in 1910 to Röntgen, "on very many things and, in the nearly 17 years of our contact, have lived through much together. We both love a quiet

Dr. Baltzer is affiliated with the University of Bern, Switzerland. This is a translation of an article based on a lecture given at the centenary of Boveri's birth, before the Physikalisch-Medizinische Gesellschaft and the Zoological Institute of the University of Würzburg on 4 November 1962. The article was originally published in *Naturwissenschaftliche Rundschau*, Stuttgart, June 1963, Supplement No. 87 of the *Verein Deutscher Biologen*. The translation, by Curt and Evelyn Stern, Berkeley, California, is offered as a tribute to the memory of Theodor Boveri and as an expression of admiration for Dr. Baltzer on the occasion of his 80th birthday.

existence, in beautiful natural surroundings if at all possible, with a few close friends with whom one can talk or be silent as one needs to." In Würzburg one of his first doctoral students, Spemann, also soon moved into friendship with Boveri. Eight years younger than he, Spemann remained active in Boveri's institute for many years after completing his doctorate. Between the two investigators there was an intensive scientific give and take, which continued in letters after Spemann was called to Rostock.

Let us return, however, to Boveri's personal development. In 1885, immediately after getting his Ph.D., Boveri was given a 5-year fellowship, the Lamont stipendium, which at that time was an extraordinary piece of good luck. It made him a "free man"—free in the sense that he could follow his bent, without considering where his bread came from. In that same year Richard Hertwig took over the directorship of the Zoological Institute in Munich, and Boveri switched over from the anatomy department to him. Hertwig, 12 years Boveri's senior, suggested to him that cell research was a promising field of investigation. Therewith the area was defined in whose development and growth in depth Boveri from then on was to participate to the maximum. According to his own formulation, he wanted to analyze "those processes whereby a new individual with definite characteristics is created from parental generative material" (1910). In these modest terms is expressed one of the important problems in biology, belonging not only to cell theory in a narrow sense but also to developmental physiology and genetics. The problem found in Boveri an equally many-sided leading investigator, for in him were united not only the capabilities of a microscopist and experimenter of first rank but also those of a theoretician and critic of great stature. His review of the constitution of the chromatin in the cell nucleus, at the Würzburg Congress of the German Zoological Society in 1903, gives impressive testimony of this.

An additional factor exists for the biologist: his counterpart, the living substance to be investigated, which has a will of its own. It is completely characteristic of Boveri, as an investigator pressing forward and in depth at the same time, that he developed nearly all his scientific work around two objects of study. Through the basic work of

Fig. 1. Theodor Boveri, about 1907.

the Belgian Ed. van Beneden in 1883 he was led to the investigation of the egg of the roundworm (*Ascaris megalocephala*), which forms only a few large chromosomes in its first mitotic divisions. Through the brothers O. and R. Hertwig, Boveri was led to the sea urchin egg, on which O. Hertwig had made his classic fertilization experiment in 1875. This marine material was peculiarly suitable for a further experimental analysis. It took Boveri again and again, and always with new formulations of the problem, to the Zoological Station in Naples. Here he worked for the first time in 1887, and for the last time in the year 1914. After the death (in 1910) of the founder of the station, Anton Dohrn, whose friend he was, Boveri gave a memorial address that belongs among the finest documents of biographical-scientific literature.

Although Boveri published over 20 papers on sea urchin eggs, during his Munich years, *Ascaris*, which he could obtain locally, was in the foreground. Here at the Munich Zoological Institute there appeared in the years between 1887 and 1890 the three first great cell studies. The second of these, a fundamental paper of 200 pages (published in 1888), contains decisive proofs of the maintenance of chromosomal individuality. Above and beyond this, the role of the centrosome is followed, and a penetrating analysis is given of the interplay of cytoplasmatic and chromosomal processes during nuclear division (dualism of mitotic processes).

The third study (1890) develops the problem of individuality further, and presents in particular the generalized proof that the chromosome sets of the maternal and paternal nuclei are morphologically and physiologically equivalent during development, a fact that later became decisive in the explanation of Mendelian inheritance.

Such successes put Boveri, in the space of a few years, in the forefront of cytologists. His friendship with the American E. B. Wilson originated during this period, when the latter, attracted by these studies, came to work with Boveri in Munich. To express his gratitude Wilson dedicated to Boveri his book on the cell, one of the most significant and outstanding books on the subject to appear in the next 30 years.

It might be mentioned that also during these years Boveri succeeded in discovering the Amphioxus kidney, sought for in vain by other investigators. In so doing, this schematically simple relative of the vertebrate brought into bright relief his gift for comparative anatomy.

Then in 1890 he suffered a severe depression. Boveri rightly considered himself as belonging to that group of persons "who can live only at the limit of their ability to achieve." For a full year he had to give up all scientific work. His letters to his brother Walter present a clear picture of his situation. "My brain is as if frozen and every bit of intellectual activity—in which category I currently consider letter writing—is forbidden me. . . . I am continually in such a bad way that I can make no decisions and become altogether imbecile. Every activity fatigues me, and so I sit or lie somewhere and in my thoughts seek out as many unpleasant things as possible and in the process paint them beautifully black." Then a month later: "Since yesterday I have been in Munich and here, where I have been accustomed to working for the past nine years and now run around stupidly, I feel so unhappy that I want to leave as soon as I can." He subsequently entered a sanatorium for cure. Months later he began to recover. Nevertheless, with all his humor, he remained a man subject to depressions.

His illness was of more serious import because his future was still uncertain and the stipend was coming to an end. "It seems," says Pauly, "as if fate slept." Boveri had turned down a teaching job in the United States. A position offered him as associate at the Zoology Department of the Museum in Munich would have forced him away from the direction of his special talent. Then, unexpectedly, the professorship at Würzburg became free. More than anyone else, Sachs, the excellent botanist in Würzburg, took up Boveri's cause. On the 22nd of March, 1893, at the age of 30, Boveri was called as professor and director of the Institute in Würzburg, whose university thus gained one of the greatest biologists of his time. The university was able to hold him, for Boveri remained true to his Frankish university until his death, despite his many opportunities to move elsewhere. With the call to Würzburg his career as an investigator was assured.

Chromosome Theory of Inheritance

At this point let us turn to one of the fundamental parts of Boveri's work, the chromosome theory of inheritance. This theory states that the genes which an individual receives from his parents are located in the chromosomes and are transmitted by these from generation to generation. Boveri is one of the founders of this now uncontested doctrine. Today, this theory is still undergoing development, having been carried into cytogenetic and biochemical areas. In the older period of morphology and physiology which lasted from 1885 to 1902, when Mendelian studies became established, Boveri was decisively involved in three basic steps.

The prime prerequisite of the theory was recognized by Rabl and Boveri in the years 1885–1888. They demonstrated that the chromosomes are individualized continuous bodies in the nucleus and in the cell. It was then Boveri, in particular, who 14 years later (between 1902 and 1907) proved that the chromosomes are not just bearers of genes in general but that different chromosomes carry different genes. Meanwhile, Mendelian genetics had begun (1900). Soon afterward, in 1902, Boveri in Germany and Sutton in the United States showed the connection between the chromosome theory and the results of Mendelism. We shall consider these three phases in some detail.

Already, during the period 1880–1885, several authors had formulated the assumption that the chromosomes have something to do with heredity. This was suggested by the regularity with which the chromosomes are formed at each cell division and become transmitted with nearly mathematical precision. However, the requirement for continuity, to which any genetic substance has to submit, did not seem to be fulfilled by the chromosomes, for during the so-called resting period of the nucleus, the interkinesis, they dissolve first into threads then into a diffuse nuclear mass of fibers. It was Boveri who succeeded in proving accurately that in *Ascaris* the chromosomes continue their existence in specific regions in this diffuse nuclear mass, and that after interkinesis they reappear from these very regions. I shall not go into details. A figure may suffice (Fig. 2). It shows two sister nuclei which, after their diffuse phase, both repeat the position of the chromosomes which was derived from the preceding division. This position varies from case to case but is always congruent in the two sister nuclei. To prove this congruence put high demands on the microscopist, so that at first Boveri had only a few clear cases. Despite the narrow factual base he leaped far ahead with his theoretical formulation and turned out to be right. Such instinctive assurance in the weighing of facts and audacity in theoretical interpretation are found united to an unusual degree in Boveri's nature. "I regard the chromosomes," he wrote in 1887, "as the most elementary organisms which carry on an independent existence within the cell." Thus, the chromosomes as specific continuous structures were sharply contrasted with all other nuclear and cellular elements, and the way was cleared to interpret them as carriers of the hereditary substance. Boveri's further demonstration (1890) that equal chromosome assortments derive from egg and sperm nuclei provided a further important base for this concept. There was no lack of contrary opinions. But the facts ultimately silenced them. It is characteristic of Boveri's persistence that 20 years later (in 1909) he proved the individuality of the chromosomes once more in all elegance when he came across unusually favorable *Ascaris* material. The drawing reproduced in Fig. 2 is taken from that second paper. To be sure, he had to admit that there are limits to the validity of his type of morphological demonstration, which only furnishes probabilities for the theory of individuality, not the kind of proof that is "required in physiology."

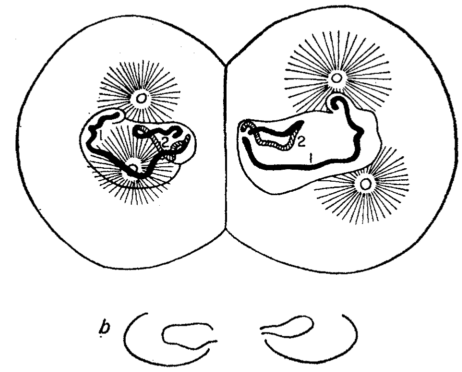

Fig. 2. *Ascaris megalocephala*, var. univalens with two chromosomes. (*a*) Egg in two-cell stage; the chromosomes in the two nuclei have equivalent positions. True length of the chromosomes, about 0.025 millimeter (about × 1060). (*b*) Position of the chromosomes, repeated schematically. [Boveri, 1909]

There remained two possibilities within the concept of the chromosomes as carriers of hereditary factors. Either each chromosome was a carrier of the totality of hereditary material, a view prevalent until 1902, or this material was distributed as separate units over the several chromosomes. Expressed in modern terms, the second alternative meant that different chromosomes are genetically different. As a result of his experiments on dispermic sea urchin eggs, Boveri reached a decision in favor of genetic diversity of chromosomes. In a highly oversimplified way one might say that in sea urchins one kind of chromosomes contains genes for skeletal formation, another kind, genes for pigmentation, and so on.

The method of proof for this idea was quite extraordinary, as is shown by the fact that neither Driesch nor E. B. Wilson, who also had worked with dispermic embryos, had conceived of Boveri's explanation. Moreover, the proof was gained quite independently of Mendelian analysis. As early as 1888, Boveri had found fertilized eggs of *Ascaris* which had formed, not the normal two, but four mitotic poles. The important point was that in such tetraster cells the dividing chromosomes are distributed unequally to the poles. One of his *Ascaris* cases is reproduced in Fig. 3. Two asters receive one chromosome only, one gets two, and the last gets four. When such an egg continues development its blastomeres, too, will get unequal numbers of chromosomes. If, now, the chromosomes are genetically nonequivalent, then during further development there should originate defective organs in individual areas or in the whole embryo. For various reasons this cannot be tested in *Ascaris*, and Boveri needed a more favorable material. He found it in sea urchins.

Sea urchin eggs can be fertilized artificially. If one uses much sperm, dispermic eggs are produced, due to simultaneous fertilization by two sperm (Fig. 4*a*). The result is a tetrapolar, or sometimes tripolar, mitosis with unequal distribution of the chromosome content, as in *Ascaris*. In such sea urchin eggs development proceeds. The tetraster eggs cleave immediately into four cells, at a time when normally fertilized eggs have formed only two cells (Fig. 4*c*). Correspondingly, the triaster cells produce simultaneously three blastomeres (Fig. 4*e*). Cell number thus corresponds to the number of poles, and the embryo consists of quarter- or third-regions which were derived from single initial cells. One picks these initial four and three blastomere eggs—*Simultanvierer* and *Simultandreier*—out of the mass of normal two-cell eggs and cultivates them in isolation. If different chromosomes are carriers of different genetic properties, then, in consequence of their unequal distribution, defects will arise. However, defects are not to be expected if all the chromosomes are equal transmitters of the total genetic material. Figure 5 gives a clear-cut example: a triaster embroyo, at the stage of the pluteus larva, which lacks all skeletal elements in exactly one-third of its body.

Apart from such sectorial deficiencies, the high frequency of pathological development also pointed clearly to a nonequivalence of different chromosomes. The haploid chromosome number in these sea urchins is 18. Both the tetraster and the triaster eggs come from dispermic fertilizations. They both have, therefore, three chromosome sets. In tetraster eggs these are distributed to four, in triaster eggs to three, poles, but not in even fashion. One of the cells may receive more chromosomes than normal of one kind, another none of this kind. It may be computed, either by means of a game of chance or mathematically, that, given a random distribution of chromosomes in 11 percent of the triaster eggs, each of their cells will be provided with each kind of chromosome. Thus, in 11 percent of the triasters normal development may be expected. Among the tetraster eggs such a favorable distribution of chromosomes hardly ever occurs. The experimental data accord well with these expectations. Together with his wife, Boveri isolated 719 triaster eggs and obtained 79 pluteus larvae—about 11 percent. On the other hand they cultivated 1500 tetraster eggs and got only one pluteus.

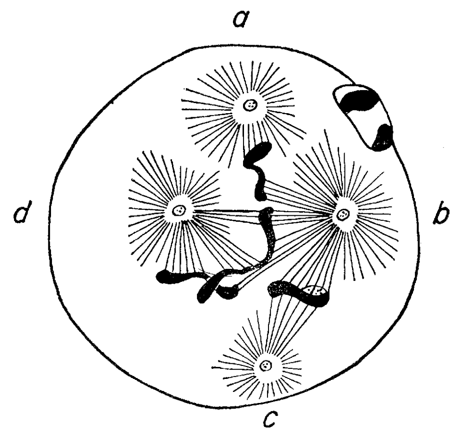

Fig. 3. *Ascaris*, tetraster egg. [Boveri, 1888]

I shall not enter into further details. If I have reported so much about this experiment the reason is, apart from its basic significance, that it has nowadays disappeared from the textbooks, those all too "unhistoric organisms." Goldschmidt's reproach to the present generation is justified. "It is hardly understandable," he wrote in 1956, "that many textbooks of genetics written nowadays omit mention of this classic." This is reason enough to bring it up again on the occasion of the master's 100th birthday.

Personal Traits

Three traits of Boveri's are especially clearly discernible in this experiment. One is his strongly visual nature, to be seen in his paintings and also apparent in his proof of the individuality of the chromosomes. Boveri did not start with abstract concepts—like, for instance, Weismann from his "ids" or Driesch from his entelechy—but always from visible objects. A second trait is his predilection for spontaneously occurring exceptions offered freely to him by nature, without complex machinery and without the "levers and screws" whose power Goethe's Faust had doubted. The dispermic sea urchin eggs were in this class of exceptions, still natural enough to develop and clearly abnormal enough to permit deeper analysis. And third, if one designates as intuition the capacity to combine into a new productive unity, through a prelogical thought process, data apparently quite foreign to one another, we have in Boveri's experiment an excellent example. The most disparate observations, such as unequal distribution of chromosomes in *Ascaris*, poor development of dispermic sea urchin eggs, and persistence of irregular chromosome numbers, once established—observations which, in part, were separated by more than a decade—were all brought together under the assumption of qualitative differences among chromosomes and connected by a conclusive experiment.

The first publication on the dispermy experiments appeared in 1902. Simultaneously, the third phase of the chromosome theory began. Very quickly the facts about chromosomes were joined with the concepts of Mendelism, whose results had been obtained by means of hybridization without relation to cytological findings. Several different biologists were instrumental in this synthesis, apart from Boveri, particularly the American, Sutton. This joint triumph of two branches of biological research was characterized in 1903 by Boveri as follows: "We see here that two areas of study which developed quite independently of each other have yielded results which are as harmonious as if one had been derived theoretically from the other." The probability is "extraordinarily high that the characters dealt with in Mendelian experiments are truly connected to specific chromosomes." With this recognition the chromosome theory of inheritance had reached a preliminary conclusion. Today it seems hardly understandable that Boveri's views at first were met with strong skepticism. In his *Zellenstudien VI* (1907) he dealt critically with his adversaries, notably with Driesch, Herbst, O. Hertwig, and others. E. B. Wilson, on the other side, who in the meantime had become the leading American cytologist, accepted Boveri's work with immediate enthusiasm. "Your completely new result," he wrote, "has become of fundamental significance for our whole view of inheritance. You furnished the long-sought exact proof of the direct influence of the nucleus of the chromosomes on morphogenesis and development."

Later Development of the Theory

The presentation would be incomplete if it did not briefly touch on the way in which the chromosome theory of inheritance developed further after Boveri's death.

Mendelian studies soon demonstrated that, in all multicellular organisms, the number of independent hereditary factors, the genes, is so very large that the chromosomes must be carriers of numerous different genes. The fruitfly *Drosophila* furnished an object where Mendelian analysis could be carried out simultaneously with studies of chromosomes. This resulted in the theory of the linear arrangement of genes which corresponds with the arrangement of specific, constant thickenings along the chromosomal thread, just like beads on a string. Further, it became clear that each kind of chromosome has its own genic series—or, to stay with the metaphor, its own unique string of beads. Thereby Boveri's theories of the genetic differences among and the individuality of chromosomes were confirmed in a greatly deepened and highly impressive manner. If one considers that Boveri died in 1915 at the age of 53 years, one can only lament the fact that he did not experience this development.

Since then a new phase of analysis, based on experiments with unicellular forms and viruses, has proved that the essential genetic part of the chromosomes consists of deoxyribonucleic acid, DNA. This is a chainlike macromolecule composed of phosphoric acid and sugar (deoxyribose molecules) and purine and pyrimidine bases in specific sequences for each species. Again, the main parts of Boveri's views have taken their place within these modern insights.

Like the chromosomes, the DNA molecules must be regarded as individuals. Here, too, qualitative differences exist, and the theory of the replication of mother chromosomes into identical daughter chromosomes has its complete parallel in the replication of the DNA chains. It is, however, not possible to retain without restriction Boveri's opinion that the chromosomes are independent—that is, autonomous—structures within the cell.

The possibility and significance of such a successful biochemical direction was discussed by Boveri half a century ago. In his aforementioned Würzburg report of 1903 (enlarged in an independent paper in 1904) his attitude was somewhat skeptical and yet prophetic. I shall quote, in slightly abbreviated form, this interesting passage: "Friedrich Miescher, the eminent founder of cytochemistry (he was the discoverer of the nucleic acids), prophesies in one of his last letters of 1895 that powerful battles will occur between the morphologists and biochemists of the 20th century. His whole work is testimony of his conviction that victory will fall to his science. The morphologist himself could not think of a better goal than carrying the morphological analysis to a point where its final elements are chemical individuals."

We have thus followed one of the great lines in Boveri's work; let us call it the chromosome line. One strand has unobtrusively accompanied this line. In 1897 a student of Wilson's, Miss O'Grady, came to Würzburg in order to work under Boveri. In 1898 she became his wife, and as a zoologist became his most important collaborator, particularly in the dispermic experiments. No less important, she was his energetic helper in life in general, in health and in illness. In 1900 a daughter was born to them. She became a very well-known writer.

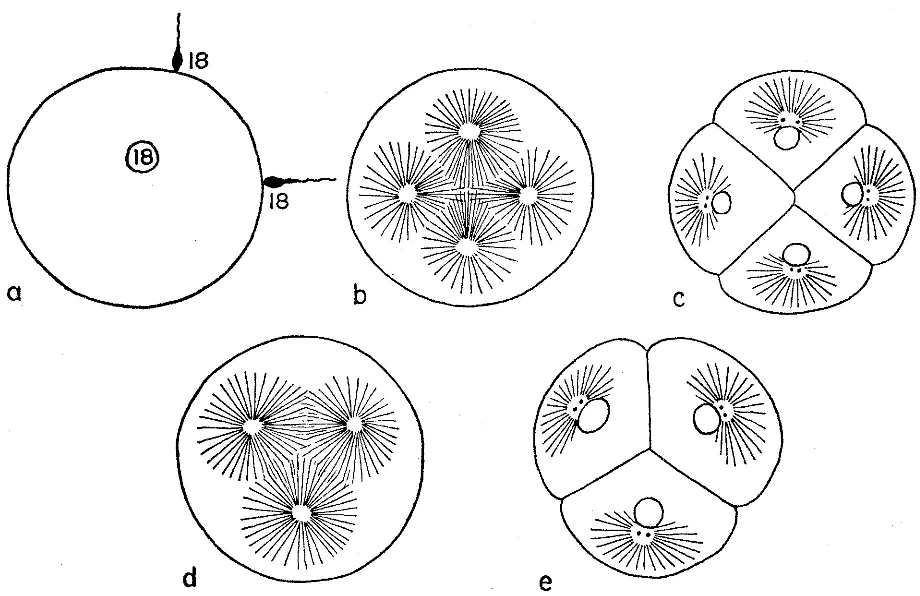

Fig. 4. Cleavage in dispermic sea urchin eggs. (*a*) Fertilization of an egg with two sperm, shown schematically. (*b* and *c*) Tetraster and resulting simultaneous cleavage into four cells (*Simultanvierer*). (*d* and *e*) Triaster and resulting simultaneous cleavage into three cells (*Simultandreier*).

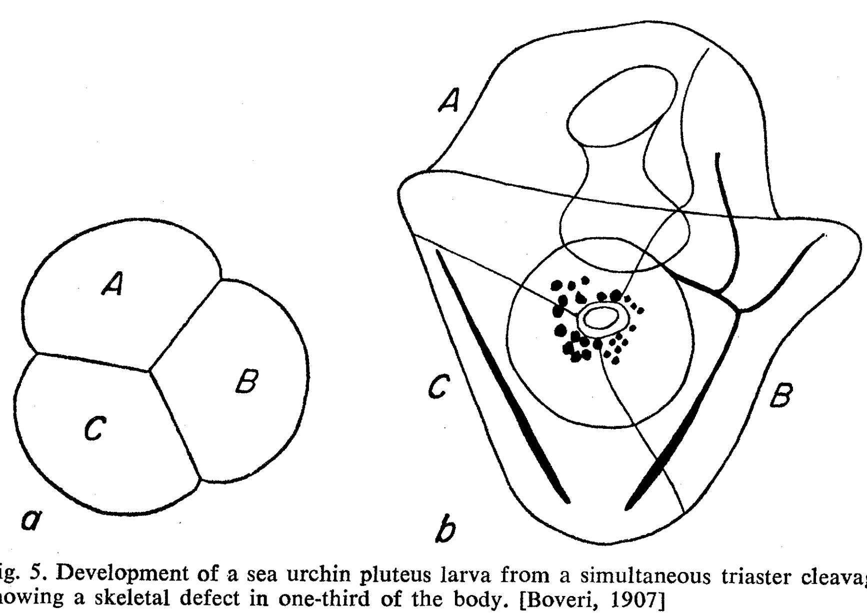

Fig. 5. Development of a sea urchin pluteus larva from a simultaneous triaster cleavage, showing a skeletal defect in one-third of the body. [Boveri, 1907]

Studies on Cytoplasm

Let us now turn to the studies on cytoplasm. The fertilized egg cell consists of a nucleus containing highly organized chromosomes and a complex cytoplasm. In the formation of the nucleus both parents are almost equally involved, but in that of the cytoplasm it is nearly exclusively the mother. It is testimony to the outstanding qualities of Boveri and to his sense of balance among problem areas that the overwhelming importance of the chromosomes as the genetic material did not divert him from the problem of the significance of the cytoplasm.

In this area, too, we are indebted to him for a decisive contribution which is still in the center of interest. The initial stimulus was provided by the discovery in 1888 that in *Ascaris* only the prospective germ cells retain the typical long chromosomes but that the other cells, the soma, lose part of their chromosomal material by the process of diminution. These first observations of the 1880's were followed by the proof, not final until 1910, that the chromosomal changes are determined by the cytoplasm. Thus, the process of diminution became "a simplest example for the way to interpret the mutual interaction between cytoplasm and nucleus during ontogeny: how the very slight inhomogeneity of the egg cytoplasm can lead to the tremendous differences of the developing cells by means of release actions on the nucleus and by subsequent reactions of the nucleus on the cytoplasm." With this concept, which took the cytoplasm as its starting point, the problem of embryonic differentiation was posed in a new way. Again, the decisive material was the development of dispermic eggs.

Boveri's results stood in opposition to Weismann's hypothesis of autonomous, unequal hereditary divisions of chromosomes, with which its author attempted to explain embryonic differentiation. Boveri's insight constituted the first step toward the clarification of an apparently vicious circle. Contrary to Weismann's hypothesis, the invariance of chromosomal replication in mitosis led to the conclusion that all cells at first receive the totality of genes. Whence, if not from the cytoplasm, should differentiation into different cell types derive? Boveri said occasionally that, with his insight into diminution, he had originally believed he had the philosopher's stone in his possession but that this did not prove to be true. Indeed, he did not succeed with his *Ascaris* work in going beyond the first fundamental recognition of the influence of the cytoplasm on the nucleus. Only very recently, about 50 years after Boveri's paper of 1910, has a further clarification been accomplished. Once again the course of events shows what importance a new test object may have for the solution of an old problem. In this specific case the deepened analysis has been made possible by studies of the salivary-gland chromosomes of *Drosophila* and related flies (see *2*).

No detailed presentation of this advance is justified here. It is, however, impressive to see how today, in the wake of Boveri's general findings of 50 years ago, a new experimental research period has set in, which now provides us with far more accurate views of the action of genes and of their collaboration with the cytoplasm.

At Würzburg

The limited space which remains will be devoted to Boveri's role as director of the Würzburg Institute and his part in the founding of the Kaiser Wilhelm Institut für Biologie, from which the present Max-Planck Institutes für Biologie originated.

All of us, predoctoral students and guests of the Würzburg institute, together hardly a dozen people, were housed in a large, long laboratory. Thus, we formed only a small "school" with an organization which, looked at from today's vantage point, had an enviably simple organization. The predoctoral students were the more permanent group: it took them about 2 years to complete their theses. The guests, mostly Americans, usually remained for shorter periods, not always to the liking of the chief. Since at the end of their stay they naturally wanted to carry home a finished manuscript, their demands on Boveri's time were often excessive. "They are true leeches," he once wrote to Spemann, "I have now resolved not to accept anyone for less than a year." Most doctoral theses were concerned with microscopical studies, often based on material which Boveri himself had collected during his experiments with sea urchins in Naples or with *Ascaris* in Würzburg. Thus it was a one-sided "school." Developmental physiology was hardly represented at all, notwithstanding the presence of Spemann, who became a classical figure in this field. However, in its way this school was not to be surpassed. Once or twice each day the chief appeared to make the rounds at the lab tables. He placed the highest importance on seeing for himself everything which was destined for future publication. He walked from table to table, asking whether something new was to be shown. If there was "nothing new" he quietly passed on. Here as elsewhere he knew how to wait. But if one gave an affirmative answer to his question, then he gave his time and patience and wanted to inspect the new finding carefully. His pleasure in microscopical analysis was clear. After this he inspected the drawings, and since he himself was an outstanding draftsman his demands were not small. He had an uncanny ability to find quickly the essential aspects in the material. Often he still remained standing after having made his observations and discussed the finding, reticent and yet giving fruitful counsel. I still see his figure before me. With his quiet manner and penetrating eyes he made a deep impression. Moreover, with all his personal participation he was by no means a schoolmaster. Accuracy, carefulness, reliability, and dedication to the object of study were the qualities which he desired above all else in his doctoral students.

When the student had studied the microscopic material for a year or a year and a half and had drawn accurate figures, the time came for synthesis and writing. Spemann, in his autobiography (*1*), has described the deep impression he received from Boveri in this phase—how Boveri stressed impressively: "You must consider writing as an art." Still more frequently, in my own experience, he would say: "You must separate quite sharply the description of facts from their interpretation." This of course was education leading to clarity of mind, and if the beginner did not immediately succeed in achieving this clarity in his text Boveri would mercilessly demand a reworking. And if he found that one had glued together old parts of the manuscript with corrected new sections, he might say ironically: "I see, you write your paper with paste and scissors" [*mit Kleister und mit Schere*].

Such an apprenticeship, particularly since it took place in a workshop where several journeymen were charged with related tasks, forms not only the scientist but also the personality—insofar as characters can be formed. It was natural for any of his students who later had students of their own to pass on a part of this experience to the next generation.

Founding of Kaiser Wilhelm Institut

It was mentioned earlier that numerous universities wanted to get a man like Boveri away from Würzburg. But he was a sessile person and liked neither mass organization nor the limelight. The first call to a new post, he used to say, is pure joy, all subsequent ones evoke mixed feelings. When, in 1911, the University of Freiburg wanted to offer him an appointment he was tempted by the beautiful location and the attractive view of the Rhine valley and of the Kaiserstuhl mountain. He wrote to Spemann as follows: "In any case I shall consider the matter carefully. If I find that I can install myself there comfortably then I may decide in these my old days [he was 49 years old] to start once more all over as homo novus." Then a month later: "The Bavarian ministry of Education was so accommodating (the Baden ministry no less!) that after having been torn for a long time by inner distress I have decided to remain in my homeland." "I shudder when I hear of the number of people who want to do their doctoral theses [in Freiburg]. I believe that it would be necessary to renounce all personal research if one wanted to carry out this task properly. Otherwise, Freiburg would indeed be a fine place."

The greatest temptation came in the following year when, in September 1912, he was offered the task of devising the plans and taking over the leadership of the then-to-be-founded Kaiser Wilhelm Institut für Biologie in Berlin-Dahlem. Numerous letters to Spemann furnish a clear and unadorned picture of the negotiations. From the beginning Boveri was indecisive. He was attracted by this new research institute and its freedom from any type of teaching obligation, as well as by the fact that a collaboration of different areas of studies was envisaged. On the other side he was afraid to throw himself into a large organization. "There are days," he wrote 2 months after the initial call, "when everything which awaits me there appears easy and beautiful, and other days when I find it directly senseless to leave this place where I am so well situated." Then, on 27 January 1913: "I am at the end of my strength. This inner struggle has lasted for four months and you cannot imagine how many matters have pressured me during this period."

It had not only been a matter of organization. There had also been the task of fighting for an increase of funds for the institute from the Kaiser Wilhelm Society, delineating the different departments, and choosing their heads. Four independent departments were to be established, according to Boveri's proposal: one for protozoology with Max Hartmann suggested as its head; one for genetics, headed by Richard Goldschmidt; one for developmental physiology under Hans Spemann; and one for biochemistry under Otto Warburg. These plans show Boveri's accuracy of judgment and his breadth. All four of the proposed individuals became investigators of the first rank, two of them—Spemann and Warburg—Nobel laureates. It was a particularly satisfying thought for him that he would work together again with Spemann in Dahlem. He wrote to Spemann (18 February 1913) how happy he was "that we, twenty years after we began working together in Würzburg, will come together once more, now in a somewhat more mature youth, in a joint great task." This hope, however, did not materialize. On 15 March 1913 he was in Berlin for detailed discussions. He returned to Würzburg ill, with a slight left-sided sensory paralysis. On 3 May 1913 he declined to accept the Berlin-Dahlem position. Subsequently, at his suggestion, Correns was charged with the directorship of the whole institute. Two days before Boveri declined the post he once more consulted Krehl, the internist, who examined him again most carefully. "I could hear clearly, behind his words that it will be better for me to stay in Würzburg and not to expose myself to the Berlin environment. Moreover, what matters most is that I feel the same myself."

It seems that Spemann wrote him after this decision that he, Boveri, with his preparatory labors and his personal prestige, had served to a high degree in the founding and development of the planned research institute. "What you are so kind as to write me," Boveri replied, "I have often in part told myself. I have gradually grown to be like that chandelier of Lichtenberg's which, while no longer lighting the place, serves at least as decoration. It has been primarily a matter of duty which caused me to approach this proposition and to live with it all winter. But I do believe now that I am released of this duty." Peace returned. On 28 June 1913 he wrote to Spemann: "After the first pain of the resignation had been overcome I experienced a feeling of quietness and satisfaction such as I had not known before. After this winter in which I was confronted with so responsible a task it is now as if I had no obligations at all any more."

A year later World War I broke out, an event that strained his already enfeebled body very much. He died on 15 October 1915, at the age of 53.

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