(Cambridge Univ. Press, New York, ed. 3, 1973).
17. F. Schrader and S. Hughes-Schrader, *Q. Rev. Biol.* **6**, 41 (1933); S. Hughes-Schrader, *Adv. Genet.* **2**, 127 (1948).
18. S. W. Brown and U. Nur, *Science* **145**, 130 (1964).
19. S. W. Brown, *ibid.* **151**, 417 (1966).
20. ——— and F. D. Bennett, *Genetics* **42**, 510 (1957); F. D. Bennett and S. W. Brown, *Can. Entomol.* **90**, 317 (1958).
21. S. W. Brown and W. A. Nelson-Rees, *Genetics* **46**, 983 (1961).
22. S. W. Brown, *Chromosoma* **14**, 360 (1963); U. Nur, *ibid.* **17**, 104 (1965).
23. U. Nur, *Genetics* **56**, 375 (1967).
24. S. W. Brown and L. I. Wiegmann, *Chromosoma* **28**, 255 (1969); M. Sabour, *Genetics* **70**, 291 (1972); L. Berlowitz, *Proc. Natl. Acad. Sci. U.S.A.* **53**, 68 (1965).
25. R. M. Kitchin, *Chromosoma* **31** (1970).
26. ———, *Genetica*, in press.
27. C. W. Metz, *Z. Indukt. Abstammungs. Vererbungsl.* **45**, 184 (1927).
28. A. M. Du Bois, *Z. Zellforsch. Mikrosk. Anat.* **19**, 595 (1933).
29. C. W. Metz, *Am. Nat.* **72**, 485 (1938).
30. H. V. Crouse, *Genetics* **45**, 1429 (1960).
31. S. M. Rieffel and H. V. Crouse, *Chromosoma* **19**, 231 (1966).
32. H. V. Crouse, A. Brown, B. C. Mumford, *ibid.* **34**, 324 (1971).
33. M. J. D. White, *Univ. Texas Publ. No. 5007* (1950); I. Geyerduszynska, *J. Exp. Zool.* **141**, 391 (1959); R. B. Nicklas, *Chromosoma* **10**, 301 (1959); C. R. Bantock, *J. Embryol. Exp. Morphol.* **24**, 257 (1970).
34. H. V. Bauer and W. Beermann, *Z. Naturforsch.* **76**, 557 (1952).
35. D. W. Cooper *et al.*, *Nat. New Biol.* **230**, 155 (1971); B. J. Richardson, A. B. Czuppon, G. B. Sharman, *ibid.*, p. 154; G. B. Sharman, *Nature (Lond.)* **230**, 231 (1971).
36. D. L. Hayman and P. G. Martin, *Genetics* **52**, 1201 (1965); in *Comparative Mammalian Cytogenetics*, K. Benirschke, Ed. (Springer-Verlag, New York, 1968), pp. 191–217; S. W. Walton, *Cytogenetics* **10**, 115 (1971).
37. M. F. Lyon, *Nature (Lond.)* **190**, 372 (1961); *Annu. Rev. Genet.* **2**, 31 (1968); *Biol. Rev. (Camb.)* **47**, 1 (1972).
38. S. W. Brown and H. S. Chandra, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 195 (1973).
39. S. E. Luria and M. L. Human, *J. Bacteriol.* **64**, 557 (1952); S. E. Luria, *Cold Spring Harbor Symp. Quant. Biol.* **18**, 237 (1953).
40. W. Arber and S. Linn, *Annu. Rev. Biochem.* **38**, 647 (1969); H. W. Boyer, *Annu. Rev. Microbiol.* **25**, 153 (1971); M. Meselson, R. Yuan, J. Heywood, *Annu. Rev. Biochem.* **41**, 447 (1972); H. W. Boyer, *Fed. Proc.* **33**, 1125 (1974).
41. E. Scarano, in *Comprehensive Biochemistry*, M. Florkin and E. H. Stotz, Eds. (Elsevier, New York, 1967), vol. 28, p. 55.
42. R. Holliday and J. E. Pugh, *Science* **187**, 226 (1975).
43. J. B. Gurdon, *Control of Gene Expression in Animal Development* (Harvard Univ. Press, Cambridge, Mass., 1974).
44. H. S. Chandra and S. W. Brown, *Nature (Lond.)* **253**, 165 (1975).
45. W. Szybalski and E. H. Szybalski, *Prog. Nucleic Acid Res.* **2**, 311 (1971); J. T. O. Kirk, *J. Mol. Biol.* **28**, 171 (1967).
46. E. Baur, *Z. Vererbungsl.* **1**, 330 (1909).
47. R. A. E. Tilney-Bassett, *Heredity* **30**, 1 (1973).
48. R. Sager, in *Genetics and Biogenesis of Mitochondria and Chloroplasts*, C. W. Birky, Jr., P.S. Perlman, T. J. Byers, Eds. (Ohio State Univ. Press, Columbus, in press); R. A. E. Tilney-Bassett, in *ibid.*
49. D. F. Callen, *Mol. Gen. Genet.* **134**, 49, 65 (1974).
50. D. R. Davies, *Heredity*, in press.
51. U. Nur, *Chromosoma* **14**, 123 (1963); *ibid.* **39**, 381 (1972).
52. S. W. Brown and F. D. Bennett, *Genetics* **42**, 510 (1957); H. C. James, *Bull. Entomol. Res.* **28**, 429 (1937).
53. L. Berlowitz, R. Kitchin, D. Pallotta, *Biochim. Biophys. Acta* **262**, 160 (1972).
54. G. Miller, L. Berlowitz, W. Regelson, *Chromosoma* **32**, 251 (1971).
55. R. Roberts, P. Myers, W. Burton, R. Sager, in preparation.
56. Supported by National Institutes of Health grant GM-13970 and American Cancer Society grant VC 32A to R.S. and by National Institutes of Health grant GM-20491 to R.K.

The Coming of Age of the Cell

The inventory of cells by fractionation, biochemistry, and electron microscopy has affected our status and thinking.

Albert Claude

Fifty years of cell research can hardly be summarized in the 20 to 30 minutes of a lecture; to expose only part of it might be unrepresentative, unfair, and altogether unnecessary, since by now you have already been informed of the essential facts and discoveries that have accumulated in the course of these years.

What I would like to do instead is to discuss with you the impact of these discoveries on our daily life and their significance for the present and the future. At the same time I will try to recall, firsthand, what has been my own experience in this century's endeavor to uncover what were, not so long ago, the mysteries of life itself.

Until 1930 or about then, biologists were in the same situation as astronomers and astrophysicists, who were permitted to see the objects of their interest, but not to touch them; the cell was as distant from us as the stars and galaxies were from them. More dramatic and frustrating was that we knew that the instrument at our disposal, the microscope, so efficient in the 19th century, had ceased to be of any use, having reached, irremediably, the theoretical limits of its resolving power.

I remember vividly my student days, spending hours at the light microscope, turning endlessly the micrometric screw, and gazing at the blurred boundary which concealed the mysterious ground substance where the secret mechanisms of cell life might be found. At last I remembered an old saying, inherited from the Greeks—that the same causes always produce the same effects—and I realized that I should stop that futile game and try something else. In the meantime, I had fallen in love with the shape and the color of the eosinophilic granules of leukocytes and attempted to isolate them. I failed—and consoled myself later on in thinking that this attempt was technically premature, especially for a premedical student, and that the eosinophilic granules were not pink, anyway. The isolation was only postponed. That Friday, 13 September 1929, when I sailed from Antwerp on the fast liner *Arabic* for an 11-day voyage to the United States, I knew exactly what I was going to do. I had mailed beforehand to Simon Flexner, director of the Rockefeller Institute, my own research program, handwritten, in poor English, and it had been accepted. My proposition had been to isolate and determine by chemical and biochemical means the constitution of the Rous chicken tumor I agent, at that time still controversial in its nature and not yet recognized as a bona fide virus. This task occupied me for about 5 years. Two short years later the microsomes, basophilic components of the cell ground substance, had settled in one of my test tubes, still a structureless jelly, but now captive in our hands.

In the following 10 years, the general method of cell fractionation by differential centrifugation was tested and improved, and the basic principles were codified in two papers in 1946. This attempt to isolate cell constituents might have been a failure if they had been destroyed by the relative brutality of the technique employed. But this did not happen. The subcellular fragments, obtained by rubbing cells in a mor-

The author is professor at the Université Catholique de Louvain, Belgium, director of the Laboratoire de Biologie Cellulaire et Cancérologie at the Université Catholique de Louvain, and adjunct professor at Rockefeller University, New York 10021.
This article is the lecture he delivered in Stockholm, Sweden, on 12 December 1974 when he received the Nobel Prize for Physiology or Medicine, a prize he shared with George Palade and Christian de Duve. The article is published here with the permission of the Nobel Foundation and will also be included in the complete volume of *Les Prix Nobel en 1974* as well as in the series Nobel Lectures (in English) published by the Elsevier Publishing Company, Amsterdam and New York. The lecture by de Duve appeared in the 18 July issue, and the lecture by Palade appeared in the 1 August issue.

tar and further subjected to the multiple cycles of sedimentations, washings, and resuspensions in an appropriate fluid medium, continued to function in our test tubes as they would in their original, cellular environment. The strict application of the balance sheet–quantitative analysis method permitted us to trace their respective distribution among the various cellular compartments and, thus, to determine the specific role they performed in the life of the cell.

Small bodies, about half a micrometer in diameter and referred to later under the name of "mitochondria," were detected under the light microscope as early as 1894. Although they continued to be extensively investigated by microscopy in the course of the following 50 years, leaving behind an enormous and controversial literature, no progress was achieved, and the chemical constitution and biochemical functions of mitochondria remained unknown to the end of that period.

In the early 1940's I began to make plans for an investigation on the distribution of respiratory pigments in cells. Considering the complexity of the problem, I realized that it should be a collaborative undertaking. A year or so before, I had collaborated with Dean Burk and Winsler in providing them with chicken tumor 10, which they used in their studies of the respiratory function in tumor cells. We started experimenting, although they were but mildly impressed by the scientific value of my project, as they told me years later. Their laboratory was located nearby, at street level in the Cornell University department of Vincent du Vignaud. I remember running across the street, handing them, through the window, each fraction as it was isolated, my share being the determination of the chemical constitution of the fractions and their respective distribution within the cell. One day Rollin D. Hotchkiss appeared, returning from a 1-year followship spent in Cambridge, England, who was delighted to find on arrival "the golden fruits on his doorstep." We were soon rejoined by Hogeboom, and later by W. C. Schneider in research on the distribution of cytochrome c in the cell and its participation in respiratory processes.

Together, the observations provided conclusive evidence to support the view that most, if not all, of cytochrome oxidase, succinoxidase, and cytochrome c, three important members of the respiratory system responsible for most of the oxygen uptake, were segregated in mitochondria. In parallel with these biochemical studies, evidence was also obtained, by tests carried out with characteristic dyes both under the microscope and in vitro, showing that the respiratory organelles and the mitochondria seen under the microscope were one and the same, a morphological discovery which would have remained meaningless, however, if we had not secured beforehand the knowledge of their biochemical functions.

Altogether, these observations demonstrated that the power of respiration exists in a discrete state in the cytoplasm, a fact which led me to suggest, in my Harvey Lecture, that the mitochondria may be considered "as the real power plants of the cell." And about the same time, with the help of electron microscopy, the microsomes became the endoplasmic reticulum.

Looking back 25 years later, what I may say is that the facts have been far better than the dreams. In the long course of cell life on this earth it remained for our age, for our generation, to receive the full ownership of our inheritance. We have entered the cell, the mansion of our birth, and started the inventory of our acquired wealth.

For over 2 billion years, through the apparent fancy of its endless differentiations and metamorphosis, the cell, in its basic physiological mechanisms, has remained one and the same. It is life itself, and our true and distant ancestor.

It is hardly more than a century since we first learned of the existence of the cell: this autonomous and all-contained unit of living matter that has acquired the knowledge and the power to reproduce; the capacity to store, transform, and utilize energy; and the capacity to accomplish physical works and to manufacture practically unlimited kinds of products. We know that the cell has possessed these attributes and biological devices and has continued to use them for billions of cell generations and years.

In the course of the past 30 or 40 years, we have learned to appreciate the complexity and perfection of the cellular mechanisms, miniaturized to the utmost at the molecular level, which reveal within the cell an unparalleled knowledge of the laws of physics and chemistry. If we examine the accomplishments of man in his most advanced endeavors, in theory and in practice, we find that the cell has done all this long before him, with greater resourcefulness and much greater efficiency.

In addition, we know also that the cell has a memory of its past, certainly in the case of the egg cell, and foresight of the future, together with precise and detailed patterns for differentiations and growth, a knowledge which is materialized in the process of reproduction and the development of all beings from bacteria to plants, beasts, or men. It is this cell which plans and composes all organisms, and which transmits to them its defects and potentialities. Man, like other organisms, is so perfectly coordinated that he may easily forget, whether awake or asleep, that he is a colony of cells in action, and that it is the cells which achieve, through him, what he has the illusion of accomplishing himself. It is the cells which create and maintain in us, during the span of our lives, our will to live and survive, to search and experiment, and to struggle.

The cell, over the billions of years of its life, has covered the earth many times with its substance, found ways to control itself and its environment, and ensure its survival. Man has now become an adjunct to perfect and carry forward these conquests. Is it absurd to imagine that our social behavior, from gregarious amoeba to man, is also planned and dictated, from stored information, by the cells? And that the time has come for men to be entrusted with the task, through heroic efforts, of bringing life to other worlds?

I am afraid that in this description of the cell, based on experimental facts, I may be accused of reintroducing a vitalistic and teleological concept that the rationalism and the scientific materialism of the 19th and early 20th centuries had banished from our literature and from our scientific thinking.

Of course, we know the laws of trial and error, of large numbers and probabilities. We know that these laws are part of the mathematical and mechanical fabric of the universe, and that they are also at play in biological processes. But, in the name of the experimental method and out of our poor knowledge, are we really entitled to claim that everything happens by chance, to the exclusion of all other possibilities?

About a year ago, I was invited to an official party by the governor of a state. As the guests were beginning to leave, the governor took me aside in a room nearby. He looked concerned and somewhat embarrassed. "Dr. Claude," he asked, "you seem to know much about life. Please tell me: what do you think about the existence of God?" The question was unexpected, but I was not unprepared. I told him that for a modern scientist, practicing experimental research, the least that could be said is that we do not know. But I felt that such a negative answer was only part of the truth. I told him that in this universe in which we live, unbounded in space, infinite in stored energy, and, who knows, unlimited in time, the adequate and positive answer, according to my belief, is that this universe may also possess infinite potentialities. The wife of the governor had joined us in the meantime. Hearing this, she seized her husband by the arm and said, "You see, I always told you so."

Life, this anti-entropy, ceaselessly reloaded with energy, is a climbing force, toward order amidst chaos, toward light among the darkness of the indefinite, toward the mystic dream of love, between the fire which devours itself and the silence of the cold. Such a nature does not accept abdication, nor skepticism.

No doubt, man will continue to weigh and to measure, watch himself grow, and his universe around him and with him, according to the ever-growing powers of his tools. For the resolving powers of our scientific instruments decide, at a given moment, the size and the vision of our universe, and the image we then make of ourselves. Once Ptolemy and Plato, yesterday Newton, today Einstein, and tomorrow new faith, new belief, and new dimensions.

As a result of the scientific revolution of the present century we are finding ourselves living in a magic world, unbelievable as little as 100 years ago: magic our telephone, radio, television by multichannel satellites; magic our conversations with the moon, with Mars and Venus, with Jupiter; magic these means which transform our former solitude into a permanent simultaneity of presence among the members of the solar system.

And here at home, thanks to these new media and the ever-increasing speed of transportation, we are witnessing a vast mutation taking place, no longer local, but of the dimensions of the globe: the birth of a new biological organism, in which all continents and all the human races participate.

For this equilibrium now in sight, let us trust that mankind, as in the greatest periods of its past, will find for itself a new code of ethics, common to all, made of tolerance, of courage, and of faith in the spirit of men.

NEWS AND COMMENT

NSF Peer Review Hearings: House Panel Starts with Critics

The first 2 days of House oversight hearings on the National Science Foundation's peer review system were dominated by the testimony of two congressmen who have been the principal critics of NSF in recent months; both pressed for major modifications of the peer review system.

Representative John B. Conlan (R–Ariz.), who has made a big issue of behavioral science courses developed with NSF support (*Science*, 2 May), asked for a "total openness" in peer review procedures, requiring, at least, that peer reviews and names of reviewers be made available to the principal investigators concerned and to Congress.

Representative Robert E. Bauman (R–Md.), author of the "Bauman amendment," which, if enacted, would give Congress authority to review and veto grants approved by NSF (*Science*, 25 April), argued for a stronger direct congressional control over research grants, although he seemed willing to depart from the letter of his amendment.

The two statements provided points of departure for discussion, but the subcommittee holding the hearings did not appear disposed to jump to conclusions. NSF officials had a chance on the third day of hearings to begin presenting their side of the case, and the hearings seemed to be settling down to a more than usually detailed examination of the inner operation of a science agency.

The hearings, which began on 22 July, are being held by the House Science and Technology Committee's subcommittee on science, research, and technology, chaired by Representative James W. Symington (D–Mo.). In his opening remarks, Symington set the general goals for the panel. He said that the subcommittee would take a detailed look at how responsibility in the peer review process was divided between peers and the NSF staff, examine alternative methods of selecting research projects for support, and seek to determine whether NSF was doing an "adequate job." Symington said the group would not take up questions such as those which have been raised about curriculum implementation and about "priority setting" between research fields and disciplines. Originally scheduled for a total of 6 days over 2 weeks, the hearings have now been extended to include an additional day on 1 August.

Conlan, the first witness, indicated that his grievance against NSF arose out of the agency's refusal to provide information on peer review of the school behavioral science course projects in which he was interested—information to which, he insists, Congress should have access.

Conlan said that, under NSF's current management practices, "they have a completely arbitrary system that is closed and unaccountable to the scientific community and to the Congress." He charged that "It is common knowledge that NSF program managers can get whatever answer they want out of the peer review system to justify their decision to reject or fund particular proposals." He added that "I know from studying material provided to me by NSF that this is an 'Old Boy's System,' where program managers rely on trusted friends in the academic community to review their proposals. These friends recommend their friends to reviewers."

Perhaps the most serious allegations against the NSF review managers came when Conlan described what happens if a reviewer fails to send back "the anticipated rave review."

"The program manager," said Conlan, "has one of two choices: He can toss out the uncomplimentary review, since he is in complete control of reviewers he selects and reviews he uses. Or he can paraphrase the negative comments, and make the review appear positive."

To illustrate his thesis, Conlan cited a recent instance in which, he said, "a program manager and his superiors misrepresented peer review comments." At issue was the Individualized Science Instructional System (ISIS) for high school students being developed at Florida State University, which Conlan said had received some $3.3 million to date from NSF.

Conlan charged that "the NSF staff appears to have purposely misrepresented reviewers' comments to the programs committee of the National Science Board in order to get approval of the current budget of $2.2 million in further funding."

As evidence, Conlan submitted for the record an NSF staff summary of the ISIS project prepared for the National Science Board when new funding for ISIS was requested and, subsequently, approved. In his testimony, Conlan quoted an extract from a review statement by Philip Morrison of MIT which appeared in the NSF summary prefaced with the sentence, "Representative of the overall tone of the reviewers' comments is this excerpt from