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JOHN W. LITTLEFIELD
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As part of our efforts to achieve these goals, we sponsor, or participate in, a variety of scientific meetings and symposia where all questions relating to birth defects are freely discussed. Through our professional educational program we speed the dissemination of information by publishing the proceedings of these meetings and symposia. From time to time, we also reprint pertinent journal articles to help achieve our goal. Now and then, in the course of these articles or discussions, individual viewpoints may be expressed which go beyond the purely scientific and into controversial matters. It should be noted, therefore, that personal viewpoints about such matters will not be censored but this does not constitute an endorsement of them by The National Foundation.

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The National Foundation–March of Dimes 1938–1977

The history of The National Foundation–March of Dimes is closely interwoven with that of medical research in the last four decades, as is seen in the programs of international conferences that the Foundation has sponsored, first in polio, later in birth defects. The Foundation's goals and research programs have coincided with the most dynamic areas of research.

In the 1940s, it was the rise of virology. This set the stage for the conquest of polio and prevention of measles, rubella and, perhaps soon, hepatitis B. Researchers also learned to use the virus as a tool of molecular genetics and apply techniques developed in bacterial viruses to animal viruses. It was phage that confirmed DNA as genetic material.

The 1950s saw triumphs of molecular biology and the coming of cell culture. From Zinder and Lederberg's transduction, through Watson and Crick's double helix, to the operon of Jacob and Monod, molecular biology owes much to the methods and insights of virologists, particularly the phage coterie. Phage pioneer Alfred Hershey put it thus: 'Perhaps the first main point to emerge from the study of . . . phages is that phage heredity and bacterial heredity are interwoven quite as closely as phage and bacterial functions; then the second main point would be that the interweaving is not inextricable.' From this intellectual ground, cancer virologists were to launch into the realm of oncogenes and proviruses.

Cell culture arose from tissue culture in the early '50s when a way was found to free cells from tissues. It became possible to count cells, grow them, clone them, and before long, hybridize them. Cell culture enabled geneticists to see human chromosomes one by one, and to find that many well-established and hitherto nameless birth defects had specific karyotypic abnormalities; cytogenetics thus entered clinical practice. Soon biochemists noted that cells in culture are like a man in miniature which can be metabolically dissected to reveal the molecular characteristics of the donor. What *E. coli* did for molecular biology, the fibroblast was to do for human genetics.

In the 1960s we saw explosive growth in immunology. The take-off point was probably the clonal selection theory, an attempt to explain how we distinguish self from not-self and how this information is continuously applied. The thymus was 'discovered' and the two-component theory brought conceptual order to study of immune response. The end of the decade saw victories of cellular engineering to correct immune deficiencies with bone marrow, fetal thymus or liver, thymus extracts, transfer factor, or combinations of these. These attempts focused the immunologists' search for ways to bypass the xenophobic rigor of immune surveillance, to make immune mechanism an obedient servant of man, and to make transplantation practical.

By 1960, biochemical geneticists were on the eve of a great adventure, though few could have foreseen what their efforts would bring in 10 years. Molecular characterization of gene products soon showed that humans differ in biochemical make-up as in physical appearance and that whenever known inborn errors of metabolism are examined, genetic variants are likely to be found. Said Barton Childs, *circa* 1959:

> Gene effects . . . are infinitely modifiable and indeed, in each individual, in greater or lesser degree, must be unique; but they are all traceable to that relationship of specificity between the genetic material and those molecules which exert qualitative and quantitative control over the metabolism of the living cell . . . The genetic method can isolate and circumscribe the problems to be studied with a high degree of refinement, but it remains for the biochemist to elucidate them.

Elucidate he did, and the results profoundly affected notions of evolution and conduct of genetic research.

By 1969, McKusick could say at the 3rd International Conference that molecular biology had freed genetics of its former dependence on pedigrees of obvious hereditary variations. We can now study genes directly in man by studying their products, proteins. Applied at the clinical level, this led to prenatal diagnosis, carrier detection, screening of newborns and high risk groups, and predictive counseling for an increasingly large number of birth defects.

By the early 1970s developmental biology was emerging as the core science of birth defects. The term refers not to a specific discipline but to a way of looking at things. It adds to medical thinking the element of time: life is development, it says, and birth defects are developmental anomalies. We need to know when genes act and in what sequences, and what can change the timetable. Each of the stages of man is an act in a scenario, and the drama in every act depends on what went on in preceding acts.

The developmental approach is most notable in studies of immunity, cancer, metabolism, hormones, and the central nervous system. The ontogeny of such proteins as collagen, hemoglobin and immunoglobulins is being intensively investigated as the best known examples of switching on and off of genes according to a preordained schedule. Clinicians are becoming aware that accelerating or reversing the process may have great therapeutic value. For more than a decade we have watched cancer biologists wrestle with alpha-fetoprotein and have only recently glimpsed its possible function – to help maintain immunological tolerance necessary for mammalian gestation.

There have been several international workshops on 'onco-developmental proteins' and a concerted search may soon be made for a developmental role of C-type RNA viruses, seemingly universal in vertebrates. Predictable too is a push to delineate fetus- or embryo-specific proteins – enzymes, hormones, receptors, membrane antigens, carrier proteins – all presumably under genetic control and subject to mutation; deficiencies or delayed appearance of these may cause many birth defects of now unknown etiology. Future historians of birth defects may hail as the turning point in teratology the recent demonstration that mouse T-locus genes

code for cell-surface antigens sequentially expressed during early embryonic development, and that T-locus mutations cause malformation in the heterozygote and embryo death in the homozygote.

All the areas mentioned have had a profound effect in shaping The National Foundation's scientific programs. In turn, these programs have contributed, sometimes decisively, to the advances recounted. The future is difficult to predict except that the unexpected is to be expected. At each international conference we have found that the preceding years have been rich in surprises. This is clear in even a cursory look at the program of the 5th International Conference, appropriately convened in Montreal, a city that has contributed so very much to our understanding of genetics and birth defects.

Foreword

It is quite possible that the major clinical reward from recombinant DNA technology, about which all of us have heard so much, will concern congenital malformations, rather than cancer, metabolic diseases, or 'genetic engineering'. This is because we cannot understand congenital malformations until we understand normal development, and here we have been blocked by an almost total lack of understanding of the structure and function of the human genome. Our ignorance of the chromosome has been reminiscent of our ignorance of DNA structure 'before Watson and Crick' 25 years ago, and perhaps even more of a bottleneck, considering the accumulated knowledge waiting to be applied to the study of development. Now, with rapid acceleration, studies with recombinant DNA and other techniques are beginning to provide a molecular model of the human chromosome, which will tell us how it stores and then progressively releases the incredibly complex information required to program development.

Due in part to our ignorance of the molecular mechanisms of development, the intellectual gap between the clinician interested in congenital malformations and the laboratory sciences which underly 'dysmorphology' is as great as that in any other specialty of pediatrics or medicine, if not greater. At the molecular level we simply cannot begin to consider ways in which development could go wrong! All the advances of molecular biology during the past 25 years are waiting to be applied to this problem. Yet presently the thoughts of the clinical dysmorphologist and of the scientist interested in development are far apart. Such an opportunity to bring the clinic and the laboratory together seems the sort of exciting long-term challenge which would provide a variety of satisfying careers.

As before, the goal of this Vth International Conference on Birth Defects was to cover broadly those advances in basic genetics, cell biology, and embryology relating to development; in biochemical genetics, somatic cell genetics, and cytogenetics; and in perinatology, clinical teratology, and clinical genetics. Although the Scientific Program Committee might be the last to learn otherwise, this meeting seemed to all of us particularly successful. The 'experts' who were present and have contributed to this volume were stellar. The afternoon sessions not included in this volume were limited to four each day, and were scheduled to avoid creating a 'conflict of interest' for the audience. The many free papers submitted were judged by a committee of experts; about 40% were considered appropriate for oral presentation, while the remainder were invited to submit posters. The workshops were chosen on the basis of interest in certain topics not represented in the morning sessions, and were more structured than before, with a number of invited speakers. A final innovation was two 'short courses' on Recombinant DNA Technology and

the Cell Surface, designed to give especially interested individuals a detailed review of these rapidly evolving areas.

For all this, we are very grateful to the members of the Program Committee, who identified the fields where progress had been made, nominated potential speakers, suggested the improvements in the afternoon programs, and then participated individually in the Conference. To all of them, and to the many other chairpersons and speakers who helped to make this Conference unusually successful, many thanks indeed!

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