Inborn Errors of Metabolism

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Preface

For those of us who were actively involved in medicine forty years ago, and later on in pediatrics in the 1950s, it was evident that a solid knowledge of biochemistry was necessary for a full understanding of various pathological conditions.

The middle of the twentieth century was a period of profound changes for pediatric medicine, during which the understanding of the pathophysiology of illnesses in general, and of genetic diseases in particular, has been totally modified.

At the end of the 1940s and during the 1950s, the advances in our knowledge were due in part to the biological applications of extraordinary technical developments such as electrophoresis and chromatography. The availability of these new techniques provided strong support for Garrod’s theory on inborn errors of metabolism.

Gibson described in 1948 the first well-documented enzyme deficiency in “familial methemoglobinemia”: the NADH-dependent reductase. In 1949, Pauling and coworkers showed that normal and sickle cell hemoglobin migrated in different ways on paper electrophoresis, and Ingram demonstrated in 1956 that this different behavior was due to the substitution of a valine residue for a glutamic acid residue in position 6 of the β chain of the globin.

Garrod’s theory in 1908 was based on his observations on alcaptonuria; only fifty years later, the underlying mechanisms of the disease were discovered by LaDu and coworkers: a deficiency of homogentisic acid oxidase. Cori and Cori pointed out in 1952 that glucose-6-phosphatase deficiency was responsible for the glycogenosis type I described by von Gierke in 1929. As early as 1934, Folling suspected that phenylketonuria was an inborn error or metabolism, but it took about 20 years to elucidate the mechanisms of the classic form of the disease: the deficiency of phenylalanine hydroxylase (Jervis, 1953).

However, hyperphenylalaninemia, which was thought to be a very simple metabolic disease, became with time a very complicated one with different variants. Phenylketonuria is a classic example of an inborn error of metabolism, not only because dietetic treatment can prevent mental retardation (as long as it is administered soon enough after birth), but also because a generalized screening program could be set up. This enables early diagnosis, which is one of the most important prerequisites for the efficacy of the dietetic treatment.

At that time, the only therapeutic possibilities were dietetic manipulations or a few palliative interventions (e.g., blood transfusion in sickle cell anemia or thalassemia). In a small number of diseases, some success could also be achieved by giving large amounts of some substances such as pyridoxine or, more recently, carnitine.

Simultaneously with the exponential increase of our knowledge concerning metabolic phenomena, very important developments occurred during the last decade in many fields of pediatrics. Widespread utilization of organ and bone marrow trans-
plantation has been facilitated by the discovery of cyclosporin in 1973 and its use in clinical practice since 1978.

The prognosis of many pathologic conditions in the 1970s has been modified by organ and tissue transplantation. In transplanting tissues or organs, our target is to replace an organ that has been destroyed by a pathological process (kidney transplantation), or to correct metabolic deficits (e.g., by auxilliary transplantation). Not only can one organ or tissue (kidney, liver, bone marrow) be grafted, but transplantations of several organs at the same time are also performed (e.g., heart–lungs transplantation in cystic fibrosis or kidney–liver transplantation in hyperoxalaturia type I).

In the last decade it is in the field of molecular genetics that the most spectacular and important advances have taken place. The time lapse between the clinical description of an inherited anomaly and the discovery of the underlying metabolic error has been strikingly shortened.

The efflorescence of research in this particular field is leading to an enormous increase in our knowledge. The way we look at inborn errors of metabolism has been profoundly modified as a result of the combined development of genetics and molecular biology. At the present time, for instance, we refer to genetic diseases rather than to inborn errors of metabolism. One is fascinated when looking back at the progress made since Lejeune and his coworkers, in 1957, discovered the exact number of chromosomes in the human cell. Now the analysis of specific sequences among restriction DNA fragments, separated by gel electrophoresis, gives us the possibility of analyzing human genes responsible for diseases. In 1978, Kan and Dozy were the first to identify a restriction fragment length polymorphism (RFLP) at the globin locus.

I am personally very much impressed, when looking at the chapters dealing with molecular genetics in the current editions of most textbooks of pediatrics, by the enormous gaps that exist between the information that can be found in these textbooks and the information available from more specialized publications in this area.

We know that inborn errors of metabolism are not infrequent. For instance, the incidence of Fölling disease more than doubled in certain countries once a clear clinical description of the illness could be given, and simple diagnostic procedures were made available. The same certainly applies to more recently described illnesses, such as peroxisomal or mitochondrial defects of fatty acid oxidation, or to the fragile X syndrome.

Nevertheless, it is becoming more and more difficult for the practicing clinician to keep his knowledge up-to-date in this field. Clinical diagnosis is usually extremely difficult because the initial symptoms of these illnesses are often very nonspecific—vomiting, convulsions, changes in behavior, hypoglycemia, and so on—while the demonstration of the defect is usually very subtle and frequently requires highly sophisticated techniques.

This volume will contribute to the practicing pediatrician’s insight into one of the major challenges of modern medicine: diagnosis, treatment and prevention of inherited metabolic diseases.

Henri L. Vis, M.D.
As a biochemically-trained physician, I was struck from the beginning of my career by the paradox of inborn metabolic diseases. Those diseases, which represent a burden of pain and distress for the patients and their parents, constitute at the same time, an irreplaceable opportunity for the scientist to understand the mysteries of life, the functioning of human cells, and the biochemical by-passes and regulation processes without which there would be no life on earth.

If one calls for the best specialist to repair an old astronomical clock, he will start by removing the pieces of this complex mechanism one after the other, and then analyze systematically the effects of each component. Only after that, will he know the exact function of each piece and, eventually, be able to repair the entire clock. The mechanisms of life are orders of magnitude more complex than an astronomical clock, and the inherited disorders of metabolism constitute experiments of nature comparable to the removal of a single piece from the complex mechanism of a clock. Thus is generated the excitement of the biochemist when confronted with disease, and the sorrow of the physician, who though appreciating the progress in the diagnosis and understanding of the pathogenesis of these disorders, remains so frequently devoid of therapeutic tools.

Among the 334 inborn errors of metabolism listed in 1988 by Victor McKusick (Mendelian Inheritance in Man, The Johns Hopkins University Press, Baltimore and London, pp. 1626), disorders responding to dietary manipulations unfortunately constitute only a minority, and for a long time antenatal diagnosis and genetic counseling have been the most efficient weapons against the others. Hardy and Weinberg's law, however, tells us that if there is one phenylketonuric (PKU) baby out of every 10,000 newborns, the PKU gene is carried by one out of every 50 adults. The overwhelming majority of mutated genes thus belong to the clinically normal population, and all our efforts concerning the families with an affected child will not significantly diminish the frequency of appearance of new patients in other families.

Fortunately, the paradox has now been partially solved. For more than a decade, great hope has risen from the progress made, first in cell, and later in organ transplantation. Without underestimating the many drawbacks of this technique, orthotopic liver transplantation appears to be a major breakthrough in the cure of inborn disorders of metabolism, because the liver is the principal, if not the only site of so many essential metabolic steps. If a new car does not start even though the electrical system is working satisfactorily, you ask for the motor to be changed. That is just what the surgeon does by orthotopic liver transplantation in Crigler-Najjar disease and in many other inborn disorders of liver metabolism.

The future lies not only in replacing, but in repairing. When will we be able to repair a defective gene? This is the challenge of the last contribution to this exciting symposium and the present book.

François Van Hoof, M.D.
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JÜRGEN SCHAUB
FRANÇOIS VAN HOOF
HENRI L. VIS
Foreword

Inborn errors of metabolism are among the very rare diseases that can be treated almost exclusively by dietetics. For this reason alone, it could not escape being chosen as the subject of a Nestlé Nutrition Workshop.

At least in the case of some inborn errors, this is one of the extremely rare examples in which mother’s milk is not the best food for a newborn, which means that more work needs to be done to develop optimal infant formulas for feeding such patients.

Interest in inborn errors peaked in the 1950s and 1960s. It was a time when technological progress allowed faster, easier, less expensive, and more accurate serum amino acid analysis; and the generalization of needle organ biopsies (liver, kidney, muscle, bone) made cellular exploration possible.

Now, at the beginning of the 1990s, there is renewed interest in the subject because of the increased possibilities for prenatal diagnosis and, if necessary, therapy. The fact that female patients are reaching the age of fecundity also raises new dietetic problems.

The subject is evolving rapidly, and this volume cannot give a definitive answer to every question. But, as our workshops are planned to allow ample time for detailed discussion, we hope this book will make an important contribution in this field.

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