Genetic Expression and Nutrition

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Genetic Expression and Nutrition

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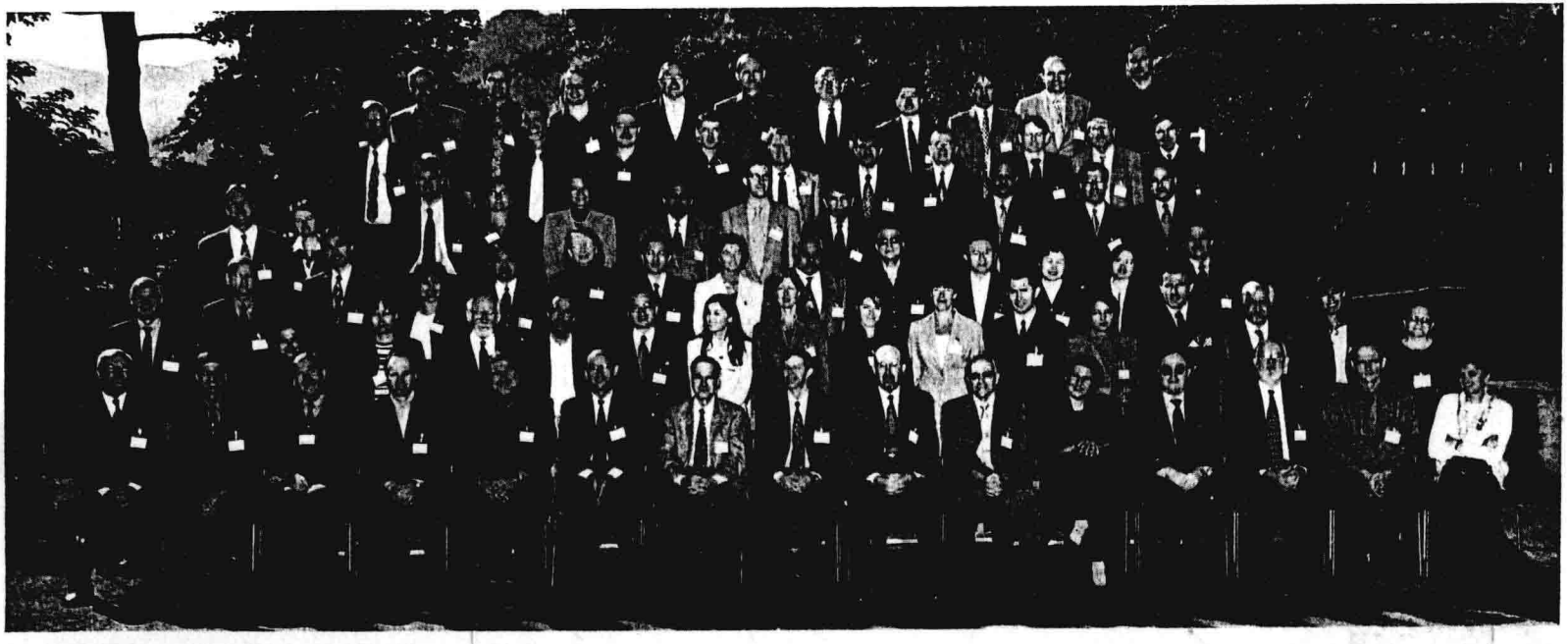

The 50th Nestlé Nutrition Workshop, Genetic Expression and Nutrition, *was held in Montreux, Switzerland, 7–11 October 2001.*

Preface

New areas of investigation and technological progress allow the testing of new and old hypotheses, raise questions, and stimulate alternative approaches. This can also be said of the rapid progress in the field of molecular biology, which has been significantly enhanced by the human genome project. However, with the mapping of the human genome it was realized at an early stage that the identification of the genetic cause of a phenotype is not the final objective of molecular research, but instead a powerful tool for gaining a better understanding of the pathophysiology leading to disease manifestation.

Although nuclear genes provide a similar potential for each nucleated cell, the actual utilization of the genetic potential varies between cells and over time, making the organism complex and conditionally able to adapt to different situations. Thus, there is a need to investigate the mechanisms of gene expression and regulation on the RNA, protein, and functional levels in cells, organs, and the whole organism, the impact of changing and complex environmental factors such as nutrition and also the potential differences between adult age and the period of growth and development.

In the past, morphological or biochemical markers have been primarily used for the understanding of normal or abnormal function in human physiology and pathophysiology. Progress in molecular biology studies starting at the gene level is now allowing the investigation of the impact of genetic factors involved in diseases. New findings tend to raise multiple new hypotheses and lead to question established models, and in this way may make their contribution to improved health and well-being.

The Program of the 50th Nestlé Nutrition Workshop held at Montreux, Switzerland, aimed at improving the understanding of nutritional physiology and biochemistry, by learning from observations in patients with genetic defects in their protein, lipid, and carbohydrate metabolism. It discussed nutritional aspects of genetic variation in populations and further included perspectives on recombinant modifications in food production, and gene therapy of inborn errors of metabolism. Distinguished experts presented data and interpretations, as well as their views on future developments, and they helped to avoid unfounded interpretations by their critical appraisal. The lively discussion with the very active involvement of a competent audience proved that the speakers had more than fulfilled expectations.

We sincerely thank the speakers, moderators, and participants for their constructive and challenging contributions. We are indebted to Mr. Ulrich Preysch and the enthusiastic staff of Nestlé Suisse SA, who hosted this most delightful event and pro-

vided impeccable logistic support, and to Dr. Anne-Lise Carrié-Fässler and Prof. Wolf Endres (Nestec Ltd, Vevey) for their excellent organizational support and helpful feedback during the planning of this workshop, which led to a most stimulating exchange of information and ideas.

Professor Claude Bachmann, Switzerland
Professor Berthold Koletzko, Germany

Foreword

These are the proceedings of a jubilee workshop—the 50th Nestlé Nutrition Workshop—since their introduction in 1980.

Knowledge about inherited metabolic disorders is growing fast, not only because of new technologies for the early detection of these diseases, but also because of the highly sophisticated differentiation of subtypes of well known defects and the development of sometimes successful treatments. In contrast, the link between our knowledge of genetic expression and our knowledge of general nutrition appeared to be rather poor. We therefore decided on the topic "Genetic Expression and Nutrition." The main objectives were to identify what insights can be gained from studying the natural course of inborn errors of metabolism, and the effects of dietary interventions in these diseases, and to see how these may be applied to people with normal metabolism or who are at risk for common diseases. At the end of this workshop we knew a great deal more about these issues, and we were in a better position to understand our present limitations in applying this knowledge practically.

I thank the two chairmen, Prof. Claude Bachmann and Prof. Berthold Koletzko, who are experts in this field, for putting the program together and inviting a group of speakers who are known to be opinion formers in the field of nutrition and genetics. Invited scientists from 25 countries contributed to the discussions that are published in the book. Mr. Ulrich Preysch's team from Nestlé Switzerland provided excellent logistical support and the participants enjoyed a taste of Swiss hospitality.

Dr. Anne-Lise Carrié Fässler from the Nutrition Strategic Business Division in Vevey, Switzerland, was responsible for the scientific coordination. Her excellent cooperation with the chairmen was essential for the success of this workshop.

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Genetic Variation of Homocysteine Metabolism and Atherosclerosis

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HOW HOMOCYSTEINE ARISES IN CELLS

Homocysteine is an amino acid that is found in mammalian cells and in the plasma. It arises in the first instance from the catabolism of the essential dietary amino acid methionine, to which it is very similar in structure (Fig. 1). This process takes place mainly in the liver as a constituent of the so-called methylation cycle (Fig. 2).

Examination of the structures of methionine and homocysteine show them to be identical except for a conversion that has resulted in the removal of a methyl group ($-CH_3$) from the former (1). *In vivo,* this transfer of the methyl group of methionine has important consequences (2). In all cells, there are dozens of enzymes called methyltransferases. As the name suggests, these are involved in the donation (or transfer) of a methyl group from the activated form of methionine, s-adenosylmethionine (SAM). The products of such methyltransferase reactions are always s-adenosylhomocysteine (SAH) and the methylated version of the substrate for the reaction (3).

The substrates for the methyltransferases vary widely and encompass a wide range of compounds that have nothing to do with each other metabolically other than that they are all methylated using SAM as the methyl donor. A recent review suggests that there are 28 different methyltransferases, each with separate functions (4). Thus, the substrates can be any of the following: proteins, which will be methylated in their arginine or lysine side chains; phospholipids, which are also methylated with the conversion of phosphatidylethanolamine to phosphatidylcholine; DNA, which can be methylated in its cytosine residues; or the hormone DOPA, which is also methylated. The functions of these methylation reactions are as varied as their substrates. Such methylations can change protein function, alter membrane characteristics, down-regulate the transcription of DNA, or even contribute to a degradation pathway.

As can be seen from Fig. 2, these widely differing methyltransferase reactions are in fact part of the methylation cycle that exists in all cells. After donation of the methyl group, with the resultant formation of the methylated product and SAH, the latter is broken down immediately *in vivo* to produce adenosine and the amino acid homocysteine. The equilibrium for the hydrolase enzyme that carries out this reaction very