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ETHNIC DIFFERENCES IN REACTIONS TO DRUGS AND XENOBIOTICS

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Preface

Many efficacious and selective drugs have become available since the mid-century. Their therapeutic use led to an increased awareness of individual differences in drug response; thus, about three decades ago, the interdisciplinary science of pharmacogenetics was born. This was followed by observations of interindividual variation in toxic response to industrial chemicals and environmental contaminants; these observations gave rise to the term "ecogenetics." At the same time, enzyme induction and adaptive processes were increasingly identified as non-genetic sources of pharmacological and toxicological variation. The occupation with variation in response to, or metabolism of, drugs and other chemicals initially concerned mainly individuals, that is to say, variation within a population was the center of interest. In recent years, it became clear that there are also differences between ethnically distinct populations in susceptibility to the effects of drugs and chemicals. This is a topic that– in spite of its medical significance—so far had never been thoroughly reviewed. This volume represents an attempt to remedy this deficiency.

The contents of this volume consist of the progress report of a Conference entitled "Ethnic Differences in Reactions to Drugs and Other Xenobiotics", held on October 3–6, 1985, at the resort town Titisee in the Black Forest of West Germany. It is a pleasure to acknowledge the recommendations of Dr. G.S. Omenn at the early planning stage of this conference, and suggestions of Dr. E.S. Vesell and Dr. D.D. Breimer which affected its final design. The conference was made possible by the Boehringer Ingelheim Fonds. To this foundation, its Director, Dr. med. H. Schroeder, and to its staff, go our sincere thanks. The foundation did not only provide the necessary financial support but also organizational and administrative help. Dr. Schroeder deserves special thanks; his personal interest and suggestions made participation in this Conference a particular pleasure; it was the 50th Conference he had held.

W. Kalow
H. Werner Goedde
Dharam P. Agarwal

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OUTLOOK OF A PHARMACOLOGIST

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The observation and interpretation of differences are the main springs of science. The subject of this conference are differences between human populations, difference which are, or did become, visible only on exposure to pharmacologic or toxic agents. A few examples have been known for many years, such as the drug-induced hemolysis of G-6-PD deficiencies in some but not all populations, or the scarcity of slow acetylators of isoniazid among - for instance - the Inuit (Eskimos) in comparison with Caucasians. Additional observations made during the last few years indicated that we can no longer take for granted an equal response to a given drug or chemical in all population. This realization leads to a number of questions: How frequent and of what kind are interethnic differences in drug response? Do they offer novel starting points for fundamental investigations? Are they of immediate clinical significance or of importance for drug development? In order to find answers to these questions it appears worthwhile to provide at this conference, first, a survey and evaluation of such differences already known. In other words, one purpose of this conference is to take stock of recorded ethnic differences in the pharmacological or toxicological response to chemicals. Second, a series of papers at this conference, and the discussions, are hoped to provide some guidance for future investigation.

Please allow me to give a personal account of the development of my interest in the topic of this conference. Early in my career as a pharmacologist, I noticed that the

chemical structures of a series of drugs determined the magnitude of response variation among rats (Kalow, 1949). It was therefore always clear to me that it is worthwhile to look for biological rules when confronted with pharmacological or toxicological variation. Later, when studying cholinesterase, I found genetic variants of that enzyme which affected the actions of the drug succinylcholine (Kalow, 1956), a finding that brought me into a field which we now call pharmacogenetics (Kalow, 1962). Several years later, I decided deliberately to commence investigations into the variability of human drug metabolism. The subjects of investigations were frequently students and staff of the University of Toronto. To make understandable what follows, I have to digress. Toronto was after the 2nd world war a city of 600,000 inhabitants. Metropolitan Toronto today houses 2.1 million, and the surrounding area along Lake Ontario is home to many millions more. The largest single ethnic group in Toronto is no longer Anglo-Saxon but is Italian. Toronto harbors one of the largest Chinese communities in North America; street names around the University are shown in English and Chinese. There are many other Ethnic groups. Much of this ethnic diversity is reflected in staff and students of the University. When we asked for volunteers for drug metabolizer studies, the responders were naturally an ethnically mixed group. We generally recorded the volunteers by the University - assigned student number, not by student name. When testing the metabolites of amobarbital, we decided to recall for re-investigation some students whose metabolite pattern differed from the average (Kalow et al., 1979); I gave to a colleague the student numbers of those to be re-invited, and to our surprise, they all turned out to be of Chinese origin. A similar situation recurred later when we investigated debrisoquine.

Thus, the crucial factor in this chain of events was the large post-war migration with its resulting mix of people of distinct origins. The second factor was my interest in variation and population differences through my (previous) occupation with pharmacogenetics. However, our observations could not be readily analysed in terms of genetics or of the environmental factors represented by diet and lifestyles. The data did not lend themselves to twin or family studies. There were too few mixed marriages, and ethnicity and diet were confounded. Many