PHARMACOGENETICS

Principles and Paediatric Aspects

by I. SZÓRÁDY

WITH A FOREWORD BY G. FANCONI

Akadémiai Kiadó, Budapest

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PRINCIPLES AND PAEDIATRIC ASPECTS

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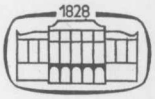
I. SZÓRÁDY, M.D., C. Sc.(med.)
Medical Director of Children's Hospital, Szeged

with a Foreword by

G. FANCONI



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F. GERLÓCZY
and
G. KISZELY

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F. SÓS

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F. MATOS

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PHARMACOGENETICS

PRINCIPLES AND PAEDIATRIC ASPECTS

To Gabriella, István

and

their Mother

FOREWORD

My first impression after having run over the proofs of this marvellous book was that the clear-cut limitation of competence of the classic sciences like clinical medicine, pathologic anatomy, chemistry, genetics, etc. belong to 40 years ago. Today every investigator in the overspecialized medical science has to cooperate with the clinician, the pharmacologist, the biochemist, the geneticist and even with the specialist in molecular investigation.

The development of chemistry increases enormously the number of new chemical substances known. It is calculated that every year 6000 new substances enter in contact with the human body: as medicaments, as cosmetics, as products for the conservation of food, as pesticides, etc. Unfortunately, many of them are pathogenous; new diseases are created; may I only mention the thalidomide disaster.

The new substances can be toxic for everyone, others produce only in some atopic individuals allergic or even idiosyncrasic reactions; rarer is the drug-sensitivity caused by enzymopathies, so that the bearer of it reacts to a drug with more or less severe disease, whereas the same drug can be very beneficial to the majority of the other humans. Today we know enzymopathies which are the cause that even important nutritive substances as lactose, fructose or galactose act as a poison (lactose- and fructose-intolerance, galactosaemia, etc.).

Today more than 700 enzymes are known in the human organism; the majority of these enzymes have many receptors; every one of them can be lacking or altered, so that different diseases can be the consequence of the insufficiency of only one enzyme. For instance, approximately 50 different variants of the glucose-6-phosphate dehydrogenase are known (see p. 87) and many of them are the cause of a drug-hypersensibility, e.g. for primaquine, etc., and the consequence is a severe acute haemolytic anaemia.

The number of special drug-sensibilities is increasing every year, therefore it is not surprising that some enzymopathies described by Prof. Szórády are completely unknown to me and are not mentioned in the newest available dictionaries either.

Especially for obstetricians and paediatricians it is very important to know that the maturation of enzymes which degrade a drug and control its action can be delated. The placenta with its 100 enzymes that form a barrier protecting the foetus

can also present enzymopathies, and therefore we must be very prudent in prescribing new drugs to a pregnant woman or to a newborn child; catastrophes like the thalidomide disaster must not repeat.

Finally, Szórády is discussing the importance of pharmacogenetic diseases in preventive and social medicine, the teaching of which is getting more important every year.

Prof. G. FANCONI
ZÜRICH
Honorary Secretary General of the
International Paediatric Association

PREFACE

On the first page of my book I would like to mention all those to whom I am indebted for assistance and encouragement in the course of my work of writing it.

First of all I owe a large debt to my father, who is also a physician, and to Prof. K. Waltner, retired director of the Paediatric Department of Szeged University School of Medicine, under whose direction I started my work. It is due to them in the first place that I have turned with interest to the field of clinical pharmacology. I am also grateful to Prof. M. Jancsó, the late director of the Pharmacological Department of Szeged University School of Medicine, who called my attention to the importance of pharmacogenetics.

I offer my heartiest thanks to Professors Lenart, Gerlóczy and Kiszely for their help in directing my work, especially to Professors Gerlóczy and Kiszely for their kindly and useful advice about problems concerned with the actual writing of the book.

I would like to express my appreciation for their assistance to the staff of the Publishing House of the Hungarian Academy of Sciences, as well as to my colleagues Dr. Madácsy and Dr. Matusovits who prepared the indexes.

I would also like to acknowledge the technical assistance given by Mrs. I. Lippay, Mrs. I. Pór, Miss G. Juharos, Miss A. Sántha and Mr. Z. Havas.

Last but not least let me acknowledge with the deepest gratitude the help of my wife who did the extensive and laborious work of the preliminary correction and editing of the manuscript and who provided encouragement and inspiration that can never be repaid.

I. Sz.

CONTENTS

INTRODUCTION

It is an experience of long standing that drug response is individual. The same drug has a more pronounced and more lasting effect in one man than in another, while in some people it may cause peculiar side-effects. Familial occurrence of extreme drug responses can sometimes also be observed.

Unusual drug responses are also known in animals. For instance, it had been observed nearly hundred years ago that certain rabbit strains are capable of eating plants containing belladonna without the slightest sign of poisoning, while others of the same species are killed by such plants.

For a long time individual drug sensitivity was considered a rarity, an accident, a caprice of nature, its occurrence in groups was either not recognized, or considered unimportant, and it was not even suggested that extreme drug responses may be governed by certain biological laws.

No satisfactory explanation was found for the unusual non-toxic drug responses to normal doses either, although after the turn of the century many of them were classified among the classic allergic or Herxheimer reactions. Still a great number of drug sensitivities of unknown origin, the so-called drug idiosyncrasies, were there to be managed, both in man and in animals.

New light was thrown on the multiplicity and divergence of drug sensitivity when attention began to be directed to group and mass incidence (family, etc.), which was no longer considered individual accident and rarity but phenomena of polymorphism, well known in biology.

For this revolutionary discovery, genetics, pharmacology and biochemistry had, however, to reach first a certain stage in their development. In the footsteps of the pioneer works of Vogel, Motulsky, Kalow and other outstanding scientists, at the beginning of the 1960's it became known that individual drug sensitivity is just as much part of the human phenotype as e.g. having fair hair or brown eyes. This discovery led to a close co-operation between the two parent disciplines: molecular pharmacology and molecular genetics, with the aim of clarifying their common problems in the light of a multitude of experimental and clinical findings.

Thus, by necessity, a new branch of science came into being for which in 1958 Vogel coined the name pharmacogenetics. The first publications dealing with the problems of pharmacogenetics did not—in fact, they could not yet—draw the exact outlines of this new branch (Motulsky, *1957*; Vogel, *1958*; Kalow, *1961*). It is still a difficult task because of the integrating character of the new discipline and the great number of related fields.

It is, therefore, justified to speak about the scope of pharmacogenetics both in a wider and in a narrower sense.

In the wider sense the subjects of pharmacogenetics are:

(1) The genetic determination and individual variability of drug responses;
(2) The mutagenic effect of drugs;
(3) Teratogenetics (Jörgensen, *1964*, *1967*; Scholz, *1967*).

Although the two last-named fields are closely related with pharmacogenetics, they are, strictly speaking, not part of it, and should, therefore, be treated separately.

Though in some plants, microorganisms, Drosophila, mammalian cell cultures and rodents, certain drugs (antipyretics, caffeine, nicotine, radiomimetic cytostatics, antimicrobial agents, etc.) have undoubtedly a mutagenic effect showing analogy with human pathology (Jörgensen, *1964*; Röhrborn, 1965; Vogel et al., 1967; Röhrborn and Vogel, 1967; Neel and Bloom, 1969; Szórády, 1970; Vogel et al., 1971), preconceptional damage of mutagenic character in the germ cell is in man due mostly to influences of other kinds (e.g. radiation). Drug effects result rather in the loss of fertility or abortion. The problem is further complicated by the cumbersome testing of drugs and the limited reliability of the tests (Röhrborn, 1965; Auerbach, 1966; Bateman, 1966; Lüning, 1966) as well as by the often neglected differences between the mutation of germ cells and of somatic cells (Marquardt, 1967).

Teratology, the other closely related discipline, studies the damaging effect of various exogenous agents on the unborn offspring (zygote, embryo or foetus). Drugs having a teratogenic effect on man (e.g. thalidomide, aminopterin, oral gestagens, androgens, corticosteroids, oral antidiabetics, iodine, quinine, tetracycline, etc.) disturb the normal growth of the foetus, causing thereby serious morphological changes resulting in congenital malformations. Other non-medicamentous agents, as well as infections, etc. may have a similar effect. There can be no doubt about the paediatric importance of the relationship between teratogenic agents and congenital malformations in the newborn (Landauer and Clark, 1964; Lenz, 1966; Smith, 1966; Kleiss, 1967; Skoupy et al., 1967; Kretchmer, 1969; Szórády, 1970). At the same time teratology can obviously not be included in the scope of pharmacogenetics, since drug effect is only one of the teratogenic factors and is definitely incidental, an individual effect which is not inherited. Teratology could become part of pharmacogenetics only if the supposition mentioned by Kalow in his book, and lately also voiced by Kalter (1968), would be confirmed, namely that hereditary factors also play a role in the teratogenic responses to drugs and their variabilities.

When these two large related disciplines are treated separately, the variability of drug response and the polymorphism of drug metabolism remain the central problems of pharmacogenetics.

Accordingly, in the light of our present knowledge, we may say that pharmacogenetics, in the narrower sense of the word, is the science dealing with the normal or defective functioning of the drug metabolizing enzymes, with the pathological states resulting from such deficiencies, and with their detection, prevention and treatment. Thus the subject of pharmacogenetics is enzymatic drug biotransformation as well as the genetics, mechanism and aberrations of drug metabolism. We could say that pharmacogenetics is the science investigating the genetic background of drug responses (effects, side-effects).

Pharmacogenetics has its genetic, biochemical and clinical aspects. This triple division is observed in several reviews and handbooks. The present monograph, as indicated by its title, has no claim to completeness; we wish to avoid the discussion of all these aspects separately, which we consider unjustified even for didactical reasons, when dealing with single enzymes.

The above definition is, however, in need of an important supplementation, namely that—as stressed by Vogel as far back as 1959—pharmacogenetics deals only with those genetically determined polymorphisms which are *primarily* revealed and made manifest by the administration of drugs. Hence pharmacogenetics can be considered 'a new science . . . , a discipline based on the study of genetically determined varia-

tions revealed by the effects of drugs' (Schimke, 1969). Those, equally genetically determined, inborn errors of metabolism whose symptoms are independent of, or not *primarily* dependent on, the administration of drugs are outside the scope of pharmacogenetics (Vogel, *1959*; Evans, 1963; Rumler, 1963; Fraser-Roberts, 1967; Schimke, 1969). The number of such non-pharmacogenetic enzymopathies known, the first of which was described by Garrod in 1902 (alkaptonuria), is today over 200 (Hsia, 1959; Schreier, 1963; Waisman, 1966; Crouch and Evanhoe, 1967; Szabó, 1967; Harris, 1968). These enzymopathies differ from the pharmacogenetic enzymopathies in that their symptoms either appear spontaneously or become manifest due to non-medicamentous agents (drinking water, diet, insecticides, etc.). Although in the case of certain inborn errors (e.g. pentosuria, Gierke's disease) there may be a changed response to certain drugs, this is only a secondary phenomenon. In the case of inborn errors in which drugs significantly aggravate the symptoms (e.g. in G-6-PD deficiency, glucuronyl transferase deficiency) it seems justified to discuss the condition both as an inborn error and as a pathological pharmacogenetic state, as will also be done in the present book.

Besides inborn errors, there are a number of other hereditary defects (e.g. haemoglobinopathies, Down's disease, diabetes mellitus, gout, glaucoma, etc.) and also other conditions which may alter drug response; these, however, will not be discussed here. Those interested in the subject find ample information in Kalow's excellent monograph.

*

Kalow (*1962*) was the first to sum up the fundamentals of pharmacogenetics. In his book *Pharmacogenetics: Heredity and the Response to Drugs* he presented an excellent comprehensive survey of the problems of pharmacogenetics including non-human aspects. Besides him only Löhr and Waller (*1966*) have treated the problem more extensively; their work which received the Hufeland prize in 1965 is still the only European review of the subject. I wish to point out, however, that neither Kalow, nor Löhr and Waller did emphasize the paediatric aspects, or did present pharmacogenetics as an integral part of clinical pharmacology.

In addition to these two books several reviews on pharmacogenetics have been published in recent years, which are listed as key references in the first part of the bibliography.

The relatively great number of publications all have the common feature that they are mostly theoretical in outlook and only a few deal with the human pathological and pharmacological aspects. The relationship between pharmacogenetics and pharmacodynamics is also only occasionally mentioned (Simpson and Kalow, *1956*). We may perhaps say that pharmacogenetics has not yet been sufficiently closely integrated into pharmacology. Consequently, in the handbooks and textbooks on pharmacology—even in such up-to-date works on molecular pharmacology as e.g. that by Holland et al. (1967)—only scanty reference is made to pharmacogenetics. Laurence, too, devotes little attention to pharmacogenetics in his book *Clinical Pharmacology* (1966). The same applies to Goth's *Medical Pharmacology* (1970). It seems that pharmacogenetics still awaits recognition as an integral part of pharmacology, its parent science. Such an attempt has been made recently by Jörgensen (*1971*). In the present monograph we shall try to introduce pharmacogenetics as a part of clinical pharmacology.

Handbooks on pharmacology, but also those on human genetics (Fraser-Robert, 1967; Penrose, 1963, 1967/68), devote no more than a few pages to the discussion of

pharmacogenetic problems. In the five volumes (!) of his up-to-date human genetics (*Humangenetik*, 1967/68) Becker discusses pharmacogenetics very briefly, devoting to the problem four pages altogether. Also Lenz (*1970*) in his *Medizinische Genetik* gives pharmacogenetics a passing treatment.

In clinical medicine, pharmacogenetics is linked primarily to paediatrics. This is easy to understand. It is obviously the paediatrist who first observes any unusual drug response. It is his duty to recognize, judge and consider these in the course of further therapeutic interventions. The early detection of the genetic constitution including the diagnosis of pharmacogenetic phenotypes depends on his skill. Therefore, the paediatrist should in the first place be acquainted with the fundamentals of pharmacogenetics, not only because he is the first doctor attending all people in the course of their lives, but also because if he commits an error, the danger will be greater for a newborn or an infant—and particularly for premature babies—than for adult patients. The newborn is much more susceptible to all kinds of noxae and, on the whole, frailer. Hence the pharmacological responsibility of the paediatrist is much greater than that of his colleagues active in other fields of medicine. There is also a third reason why paediatrics is more closely linked with pharmacogenetics than any other clinical discipline: namely, the temporarily immature, insufficient enzyme set, including that of several drug metabolizing enzymes, of prematurely born babies and of the newborn. The biochemical and clinical consequences of this temporary immaturity are the same as those of genetically determined enzyme defects. These reasons, and particularly the last one which we first pointed out (Szórády, *1967*), justify the emphasis laid on paediatric aspects in the present book.

In the European paediatric literature Wiedemann was probably the first one to deal with pharmacogenetics in his inaugural speech at the University of Kiel in 1962. It might be worth while to quote some of his statements: "*Wenn oben bereits eine Pharmako-Toxikologie der Pränatalperiode gefordert wurde, so muß an dieser Stelle meiner Ausführungen das hohe — wissenschaftliche und praktische — Interesse der Pädiatrie an der sich entwickelnden Pharmakogenetik erwähnt werden. Die Begriffe der »Konstitution« und der — so scharfsinnig von Pfaundler verfolgten — kindlichen »Diathesen« oder Krankheitsbereitschaften . . . erfahren nicht zuletzt aus dem eben berührten Bereich der heute so wichtig gewordenen biochemischen Erbforschungen eine verschärfte Beleuchtung — wobei wir übrigens nicht vergessen sollten, daß Czerny in 1909 für die entzündliche oder »exsudative« Diathese einen kongenitalen Defekt im Chemismus des Körpers angenommen hat . . .*" (Wiedemann, 1963).

It was not by chance that in the same year when Kalow's book was published a paediatrist was among the first who turned with interest towards this new branch of science and already assumed a certain relationship between the old concept 'biochemical diathesis' and pharmacogenetics.

Though some reviews by paediatrists (Rumler, *1963*; Porter, *1964*; Szórády, *1967*, *1969*, *1970*; Edwards, *1970*) and some papers on certain matters of detail of pharmacogenetics (Weingärtner, 1964; Prader, 1966) have been published recently, we are looking in vain for the treatment of pharmacogenetics as an independent discipline in the handbooks and textbooks of paediatrics. Some related problems (G-6-PD, glucuronyl transferase, catalase, etc.) are occasionally mentioned, mostly in chapters dealing with enzymopathies or inborn errors of metabolism, or with perinatal pharmacology. In this respect perhaps Nyhan's review in the second edition (1966) of *Pediatric Therapy* edited by Shirkey is the only exception. In this book of 1223 pages the new discipline is summed up on four pages; nevertheless, the fact that a separate chapter has been devoted to the subject is a positive sign. Even