ADVANCES IN PHARMACOLOGY AND THERAPEUTICS

Proceedings of the 7th International Congress of Pharmacology

General Editors: J. R. BOISSIER, P. LECHAT & J. FICHELLE

Volume 6

CLINICAL PHARMACOLOGY

Editor: P. DUCHENE-MARULLAZ

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Editor

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Clermont Ferrand

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Introduction

The scientific contributions at the 7th International Congress of Pharmacology were of considerable merit. Apart from the sessions organised in advance, more than 2,200 papers were presented, either verbally or in the form of posters, and the abundance of the latter in the congress hall is a good indication that this particular medium of communication is becoming increasingly attractive to research workers, and offers scope for discussions which combine an elaborate, thorough approach with a certain informality.

It would have been preferable to have published the entire congress proceedings within the framework of the reports. That was, however, physically impossible, and the organisers had to adopt a realistic solution by publishing only the main lectures, symposia and methodological seminars. The amount of material presented necessitated the printing of ten volumes, each volume containing congress topics regrouped according to their relevant content and subject areas. This system of division may give rise to criticism on account of its artificiality, and we readily admit that certain texts could have been placed in more than one volume. We are asking the reader to excuse this arbitrariness, which is due to the editors' personal points of view.

I draw attention to the fact that most of the symposia finish with a commentary which the chairmen had the option of including, presenting their personal opinions on one or several points. We think that such an addition will facilitate reflection, discussion, indeed even controversy.

The launching of the scientific programme for this congress began in September 1975 on returning from the last meeting in Helsinki. Long and delicate discussions took place in the Scientific Programme Committee and with the International Advisory Board. Should it be a pioneer, 'avant-garde' congress? Or one laid out like a balance-sheet? Should we restrict the congress to the traditional bounds of pharmacology, or extend the range of papers to cover the finest discipline? The choice was difficult, and the result has been a blend of the two, which each participant will have appreciated in terms of his training, his tastes, and his own research.

A certain number of options, however, were taken deliberately: wide scope was given to toxicology, from different points of view, and to clinical pharmacology, a subject much discussed yet so badly practised; the founding of two symposia devoted

to chemotherapy of parasitic diseases which are still plagues and scourges in certain parts of the world; a modest but firm overture in the field of immunopharmacology, which up until now was something of a poor relation reserved only for clinical physicians; the extension of methodological seminars, in view of the fact that new techniques are indispensable to the development of a discipline.

We have been aware since the beginning that, out of over 4,000 participants who made the journey to Paris, not one could assimilate such a huge body of knowledge. Our wish is that the reading of these reports will allow all of them to become aware of the fantastic evolution of pharmacology in the course of these latter years. If one considers pharmacology as the study of the interactions between a "substance" and a living organism, then there is no other interpretation. Nevertheless, one must admit that there exists a period for describing and analysing a pharmacological effect, and that it is only afterwards that the working mechanism can be specified; a mechanism which will permit these "substances" to be used for the dismantling and breaking down of physiological mechanisms, a process which justifies Claude BERNARD'S term, "chemical scalpel".

The reader will be able to profit equally from more down-to-earth contributions, more applied to therapeutics, and less "noble", perhaps, for the research worker. He will realise then that his work, his research and his creative genius are first and foremost in the service of Man, and will remember this statement from Louis PASTEUR:

> "Let us not share the opinion of these narrow minds who scorn everything in science which does not have an immediate application, but let us not neglect the practical consequences of discovery."

I would like to renew my thanks to my colleagues in the Scientific Programme Committee and also to the members of the International Advisory Board, whose advice has been invaluable. I owe a particular thought to J J BURNS, now the past-president of IUPHAR, who granted me a support which is never discussed, and a staunch, sincere friendship. The Chairmen have effected an admirable achievement in the organisation of their proceedings, and in making a difficult choice from the most qualified speakers. The latter equally deserve our gratitude for having presented papers of such high quality, and for having submitted their manuscripts in good time.

The publisher, Robert MAXWELL, has, as always, put his kindness and efficiency at our service in order to carry out the publication of these reports. But none of it would have been possible without the work and competence of Miss IVIMY, whom I would like to thank personally.

My thanks again to the editors of the volumes who, in the middle of the holiday period, did not hesitate to work on the manuscripts in order to keep to the completion date.

Finally, a big thank you to all my collaborators, research workers, technicians and secretaries who have put their whole hearts into the service of pharmacology. They have contributed to the realisation of our hopes for this 7th International Congress, the great festival of Pharmacology. Make an appointment for the next one, in 1981, in Tokyo.

Jacques R BOISSIER

Chairman

Scientific Programme Committee

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The Individual Factor in Drug Response

Genetic and Environmental Factors Responsible for Interindividual Variations in Drug Response

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INTRODUCTION

This symposium on "The Individual Factor in Drug Response" discusses only a few of the many factors causing differences among subjects in drug disposition and response. Such differences are exemplified by the amazing fact that the same dose of a drug given by the same route to patients of the same age and sex, suffering from the same disease, can produce toxicity in some, therapeutic effects in others but no effects whatever in still others. Thus, the old adage that one man's food is another man's poison applies to many drugs. Astute physicians long recognizing the practical problem imposed by large interindividual variations in disposition of and response to many commonly used potent drugs adjusted drug dosage in each patient in order to maximize drug benefits and reduce toxicity. This practice of individualizing drug therapy means selecting the appropriate drug for a patient and also tailoring dosage to the unique requirements of each patient.

During the past decade, major strides have been taken in identifying factors responsible for large variations among subjects in drug disposition and response. Table 1 lists some of these factors that have been identified in experimental animals where compared to man both the genetic constitution as well as the environment can be better defined and hence controlled. How these factors affect drug disposition and response is too broad a topic to cover adequately in this symposium. Moreover, at the present time we have but scratched the surface of the subject and need to learn much more. By emphasizing a few diverse aspects of current interest in the field, we hope that this symposium will draw more attention to the general problem, thereby stimulating further research on mechanisms responsible for these variations.

Quantitative Estimates of the Magnitude of Interindividual and Intraindividual Variations in Drug Disposition

Normal subjects living in a geographically circumscribed area and in a "basal state" with respect to factors affecting drug disposition often exhibit large interindividual variations in rates of hepatic drug oxidation. The magnitude of these interindividual variations can range anywhere from 3-fold to 40- or 50-fold, depending on the drug studied. Twin (1-7) and family (8-10) studies based on administration of approximately a dozen different drugs eliminated primarily by

Table 1

Variables in the external environment	Variables in the internal environment	Pharmacologic variables
Air exchange and composition	Adjuvant arthritis	Drugs
Barometric pressure	Age	acute vs. chronic administration, bioavailability, dose, withdrawal, presence of other drugs or food, routes of administration, tolerance, vehicle, volume of material injected
Cage design-materials (crowding, exercise)	Alloxan diabetes	
Cedar and other softwood bedding	Cardiovascular function	
Cleanliness	Castration and hormone replacement	
Coprophagia	Circadian and seasonal variations	
Diet (food and water)	Dehydration	
Gravity	Disease	
Hepatic microsomal enzyme induction or inhibition by insecticides, piperonyl butoxide, heavy metals, detergents, organic solvents, ammonia, vinyl chloride, aerosols containing eucalyptol, etc.	hepatic, renal, malignant endocrine (thyroid, adrenal)	
	Estrous cycle	
	Fever	
	Gastrointestinal function, patency and flora	
	Genetic constitution (strain and species differences)	
	Hepatic blood flow	
	Infection	
	Malnutrition, starvation	
	Pregnancy	
	Sex	
	Shock (hemorrhagic or endotoxic)	
	Stress	
Handling		
Humidity		
Light cycle		
Noise level		
Temperature		

hepatic metabolism revealed that in normal volunteers living in a "basal state" genetic factors are predominantly responsible for large interindividual variations in rates of drug clearance. Fig. 1 shows results of twin studies on antipyrine (2) and bishydroxycoumarin (3). Few subjects in our modern industrial urban environments remain long in a strictly "basal state," no matter how compliant they may be or how vigilant the investigators in selecting appropriate subjects. Thus, when a test drug such as antipyrine or aminopyrine is administered at regular intervals, pharmacokinetic values occasionally differ by approximately 10 to 25% from the closely reproducible values of less than 10% variation consistently obtained in each subject at most other times. Stated differently, in studies on the magnitude of intraindividual variation where repeated measurements are taken at regular intervals, most measurements vary less than 10% from the mean value; nevertheless, an occasional value will exceed 10% (Table 2). The most likely reason for this exception is that on that particular occasion the environment of the individual was altered with respect to one or even several of the multiple factors shown in Table 1 that can change rates of hepatic drug oxidation. Table 2 shows results from one of several similar experiments we performed, all with the same results. The magnitude of interindividual variability in this study on antipyrine disposition is an order of magnitude (300%) higher than the magnitude of intraindividual variability (10%).

Without strict control of many factors listed in Table 1, the magnitude of the intraindividual variability can far exceed that shown in Table 2, particularly if during the study a subject starts medication, begins smoking cigarettes or ingesting ethanol heavily, makes certain dietary changes or is exposed to such

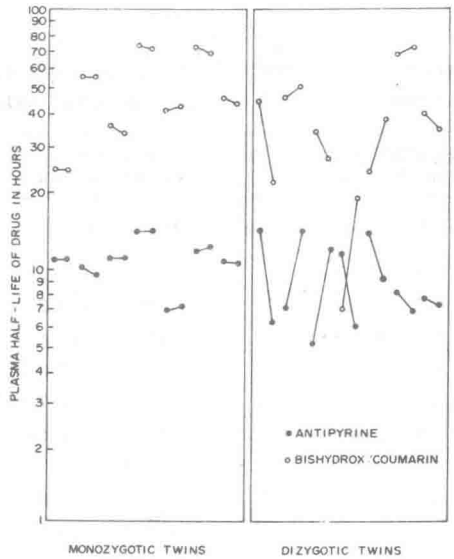

Fig. 1. Plasma half-lives of bishydroxycoumarin and antipyrine were measured separately at an interval of more than 6 months in healthy monozygotic (identical) and dizygotic (fraternal) twins. A solid line joins the values for each set of twins for each drug. Note that intratwin differences in the plasma half-life of both bishydroxycoumarin and antipyrine are smaller in monozygotic than in dizygotic twins. However, some DZ twins resemble MZ twins in having very small intratwin differences.

environmental contaminants as PCB, insecticides, etc. Experiments on drug disposition in human subjects present problems because many factors listed in Table 1 can, if not rigidly controlled, fluctuate during the course of the study. We previously stressed the need to reduce contributions by certain factors listed in Table 1 to large interindividual variations by performing carefully controlled experiments in which each subject serves as his/her own control (11) and such test drugs as antipyrine or aminopyrine are administered repeatedly to establish "basal" values.

Single Factors or Monogenic Conditions Affecting Drug Disposition and Response

Conditions inherited monogenically or as simple single factors are controlled by alleles (genes) situated at only one genetic locus. Table 3 lists more than a dozen such simple single factors or monogenic conditions affecting drug metabolism or receptor interaction. These conditions are of special interest not only because of their clear-cut mode of genetic transmission, but also because when any one of a limited number of drugs is administered to individuals susceptible because of their genotype, toxicity can occur. This toxicity arises either from accumulation of drug because of inadequate metabolism or from interaction of drug with a vulnerable site in the body. This vulnerability is secondary to a genetic defect affecting the structure and/or function of a molecule where drug or drug

Table 2

Reproducibility of Salivary Antipyrine Half-lives, Metabolic Clearance Rates (MCR) and Apparent Volumes of Distribution (aVd) in Normal Male Volunteers

Volunteer	Percent deviation from mean antipyrine half-life			Percent deviation from mean antipyrine MCR			Percent deviation from mean antipyrine aVd		
	Day 1	Day 8	Day 27	Day 1	Day 8	Day 27	Day 1	Day 8	Day 27
J.Du.	- 1.8	+ 1.8	+ 0.9	+ 1.4	- 1.6	+ 0.2	- 1.1	+ 0.2	+ 0.7
A.G.	+ 4.2	-11.3	+ 7.0	- 9.1	+ 8.5	- 0.2	- 4.1	+ 3.3	- 7.4
L.W.	0	-12.7	+11.9	- 2.0	+12.6	-10.6	- 0.6	- 0.2	+ 1.2
H.R.	+ 8.0	- 5.4	- 2.7	- 9.4	+ 4.2	+ 5.0	- 1.6	- 1.1	+ 2.5
J.Do.	- 2.7	+11.7	- 9.1	- 0.5	- 2.0	+ 2.7	- 2.9	+ 9.2	- 6.4
P.B.	+ 1.7	- 3.5	+ 1.7	-15.6	-10.8	+21.8	-14.5	- 9.7	+24.1
K.St.	- 7.5	+ 2.5	+ 6.2	- 0.6	+ 3.7	- 3.3	- 7.5	+ 8.6	- 1.9
B.P.	- 7.1	+ 8.2	0	+ 7.3	+ 0.4	- 7.8	+ 0.2	+ 7.9	- 7.9
K.Sh.	+ 3.9	- 2.9	0	-17.8	+10.3	+ 7.5	-14.3	+ 6.9	+ 7.6
M.O.	+ 5.1	- 4.1	- 1.0	+ 3.0	+13.6	-16.7	- 8.3	- 8.9	+17.3
R.S.	+ 1.0	- 1.0	+ 1.0	+ 3.4	+ 3.2	- 6.8	+ 3.0	+ 2.4	- 5.4
B.S.	+ 8.5	-18.3	+11.0	-16.6	+25.9	- 0.7	- 7.9	+ 4.9	+ 2.6

molecule interacts, as in warfarin resistance which is transmitted as an autosomal dominant trait (Table 3). Another example of this kind of genetically controlled drug toxicity is hemolysis after administration of many drugs in patients with glucose-6-phosphate-dehydrogenase deficiency, which is transmitted as an X-linked recessive trait (Table 3). In addition to conditions listed in Table 3, several inborn errors of metabolism such as diabetes mellitus, porphyria and gout are associated with abnormal drug responses. Because these disorders are caused by genetically controlled lesions in proteins not primarily concerned with drug disposition and response, they are not listed in Table 3.

Recognition that many hereditary conditions cause drug toxicity has fundamental as well as therapeutic implications. Probably many as yet unidentified monogenically transmitted defects in addition to those listed in Table 3 result in adverse reactions to certain drugs; the role of heredity in controlling the expression of allergic reactions due to hypersensitivity to certain drugs requires more investigation.

Polygenically Controlled Conditions Affecting Drug Disposition and Response

With the notable exceptions of glucose-6-phosphate-dehydrogenase deficiency and polymorphic acetylation, most conditions listed in Table 3 involve few drugs and relatively few individuals. By contrast, in the past decade new genetic factors affecting drug disposition have been shown to control how all subjects respond to

Table 3

Pharmacogenetic Conditions with Putative Aberrant Enzyme, Mode of Inheritance, Frequency and Drugs that can Elicit the Signs and Symptoms of the Disorder

Name of Condition	Aberrant enzyme and location	Mode of Inheritance	Frequency	Drugs that produce the abnormal response
GENETIC CONDITIONS PROBABLY TRANSMITTED AS SINGLE FACTORS ALTERING THE WAY THE BODY ACTS ON DRUGS (ALTERED DRUG METABOLISM)				
1. Acatalasia	catalase in erythrocytes	autosomal recessive	mainly in Japan and Switzerland, reaching 1% in certain small areas of Japan	hydrogen peroxide
2. Slow inactivation of isoniazid	isoniazid acetylase in liver	autosomal recessive	approximately 50% of U.S.A. population	isoniazid, sulfamethazine, sulfamerazine, phenelzine, dapsone, hydralazine, procainamide
3. Suxamethonium sensitivity or atypical pseudocholinesterase	pseudocholinesterase in plasma	autosomal recessive	several aberrant alleles; most common disorder occurs 1 in 2500	suxamethonium or succinylcholine
4. Diphenylhydantoin toxicity due to deficient parahydroxylation	? mixed function oxidase in liver microsomes that parahydroxylates diphenylhydantoin	autosomal or X-linked dominant	only 1 small pedigree	diphenylhydantoin
5. Bishydroxycoumarin sensitivity	? mixed function oxidase in liver microsomes that hydroxylates bishydroxycoumarin	unknown	only 1 small pedigree	bishydroxycoumarin
6. Acetophenetidin-induced methemoglobinemia	? mixed function oxidase in liver microsomes that deethylates acetophenetidin	autosomal recessive	only 1 small pedigree	acetophenetidin
7. Polymorphic serum aryl esterase activity	serum aryl esterase (paraoxinase)	autosomal recessive	several hundred individuals have been examined, yielding gene frequencies of 0.6 and 0.4	paraoxone
8. Deficient N-hydroxylation of amobarbital	? mixed function oxidase in liver microsomes that N-hydroxylates amobarbital	autosomal recessive	only 1 pedigree: screening of over 100 unrelated, normal volunteers revealed that approximately 2% were homozygous affected	amobarbital
9. Polymorphic hydroxylation of debrisoquine in man	? mixed function oxidase in liver microsomes that 4-hydroxylates debrisoquine	autosomal recessive	94 volunteers and 3 families with a frequency of homozygous affected individuals of approximately 3%	debrisoquine
GENETIC CONDITIONS PROBABLY TRANSMITTED AS SINGLE FACTORS ALTERING THE WAY DRUGS ACT ON THE BODY				
1. Warfarin resistance	? altered receptor or enzyme in liver with increased affinity for vitamin K	autosomal dominant	2 large pedigrees	warfarin
2. Glucose-6-phosphate dehydrogenase deficiency, favism or drug-induced hemolytic anemia	glucose-6-phosphate dehydrogenase	X-linked incomplete codominant	approximately 100,000,000 affected in world; occurs in high frequency where malaria is endemic; 80 biochemically distinct mutations	many different drugs
3. Drug-sensitive hemoglobins a) Hemoglobin Zurich	arginine substitution for histidine at the 63rd position of the β-chain of hemoglobin	autosomal dominant	2 small pedigrees	sulfonamides
b) Hemoglobin H	hemoglobin composed of 4 β-chains			many different drugs
4. Inability to taste phenylthiourea or phenylthiocarbamide	unknown	autosomal recessive	approximately 30% of Caucasians	drugs containing N-C-S group such as phenylthiourmethyl and propylthiouracil
5. Glaucoma due to abnormal response to intraocular pressure to steroids	unknown	autosomal recessive	approximately 5% of U.S.A. population	corticosteroids
6. Malignant hyperthermia with muscular rigidity	unknown	autosomal dominant	approximately 1 in 20,000 anesthetized patients	various anesthetics, especially halothane
7. Methemoglobin reductase deficiency	methemoglobin reductase	autosomal recessive heterozygous carriers affected	approximately 1 in 100 are heterozygous carriers	many different drugs

most drugs (1-7,12). This remarkable conclusion was suggested by results of twin studies. The subjects were normal adult twin volunteers living in different households but not receiving other drugs or compounds that can alter rates of drug disposition. The results showed that large interindividual variations in the disposition of at least a dozen commonly used drugs disappeared in monozygotic (MZ) twins (who are genetically identical) but were preserved in dizygotic (DZ) twins (who differ genetically in approximately half their total complement of genes). Family studies using bishydroxycoumarin (8), nortriptyline (9) and phenylbutazone (10) extended these conclusions by revealing a significant regression of mean offspring value on midparent value, a result consistent with polygenic control. Also consistent with a polygenic mechanism were unimodal, Gaussian distribution curves of pharmacokinetic measurements for these drugs in unrelated subjects. Nevertheless, before polygenic inheritance can be firmly established as the genetic mechanism controlling interindividual variations in basal rates of elimination of these drugs, genetic studies should be performed in families on rates of production of the major metabolites of each drug, rather than simply disappearance rate of the parent compound (13). Monogenic control should be sought. Since hepatic metabolism of each drug is complex, probably involving several distinct reactions controlled by different proteins, a more direct estimate of the function of the gene controlling a protein can be obtained by measuring rates of production of each metabolite independently of others (13). Measuring only disappearance of parent drug represents a diluted approximation of gene function because such values combine activities of several independent enzymes, thereby reflecting summated effects of genes at several different loci. Attempts have been made in

pharmacogenetics to follow the appearance of a drug metabolite, rather than simply the disappearance of the parent compound; examples of such work include a twin study of the rate of production of the major halothane metabolite (14) and another twin study on the major metabolite of nortriptyline (15). Caution should be exercised in taking urinary measurements of relatively unstable hydroxylated metabolites as precise reflections of the amount of metabolite released at the site of hepatic biotransformation. Many opportunities exist for both loss of and addition to these metabolites between their production by liver enzymes and their appearance in urine.

Family studies of drug elimination may be less satisfactory than twin studies for two reasons, the first being that the disposition of certain therapeutic agents changes with age and varies according to sex. Twin studies are by definition age corrected, but results of family studies are difficult to interpret because of the difficulty in correcting for this poorly defined change in drug disposition with age. Secondly, rates of drug metabolism can change either in laboratory animals or in man by exposure to such environmental constituents as caffeine, nicotine, 3-methylcholanthrene, 3,4-benzpyrene and various insecticides. Therefore, the closer environmental similarity of children compared to parents could partially explain changes in drug-metabolizing capacity observed in family studies. Such influences exerted by numerous environmental constituents on drug-metabolizing capacity may explain why, in one family study, values for plasma phenylbutazone half-lives were similar for healthy, nonmedicated husbands and wives.

In polygenic inheritance, alleles at several different loci on a chromosome(s) contribute to the phenotype. Hence, each gene exerts a less profound effect on the phenotype than in single gene inheritance. Furthermore, in polygenic inheritance, pharmacological responses are usually continuous, rather than discrete as in monogenic inheritance; and responses generate a single, unimodal distribution that conforms to the Gaussian curve. Individual genetic constitutions are often difficult, if not impossible, to ascertain from the phenotype, because too many steps intervene between genotype and phenotype. Instead of performing family studies which are most useful for single gene analysis, geneticists approach polygenic inheritance by comparisons of the amount of phenotypic resemblance between parents and offspring and between siblings. Twin studies are another technique used to study polygenic inheritance. Both twin and family analyses separate phenotypic variation into genetic and environmental components.

Twins are useful in examining the question of the relative contributions of genetic and environmental factors to large interindividual variations in drug clearance. With the critical assumption that no greater environmental influences are exerted on drug disposition within DZ than within MZ adult twins living and eating in separate households in a large city, an assumption that we believe was fairly well met in our twin studies, the results revealed that genetic factors are primarily responsible for large interindividual differences in rates of drug clearance from plasma. At least we were unable to identify any environmental factor that operated nonrandomly, thereby affecting predominantly either DZ or MZ twins.

Environmental Factors Affecting Drug Disposition and Response

Predominantly genetic control of large interindividual variations in rates of drug elimination among healthy, nonmedicated volunteers in a "basal state" of drug metabolism has several potentially useful implications. In the first place, since rates of drug elimination are genetically, rather than environmentally, controlled