THERAPEUTIC RELEVANCE OF DRUG ASSAYS

edited by

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FOREWORD

The desirability of quality-assay of ingestable or imbibable material has resulted in an established procedure in advanced countries. Testimony to its necessity was borne by the scandal of chateau-bottled Bordeaux *crus classés* a few years ago, a litigation instigated by the disillusioned consumers who either on the basis of absence of the expected inebriate state, or of the olfacto-gustatory caress by the bouquet or full-bodied lingering pharyngeal sensation, decided to strike a paranoid attitude, which ultimately proved to be justified.

When one proceeds from sheer pleasure to dire necessity, the question of what happens to ingested medication assumes quite portentous features. Testimony is borne to this by the transitional stage, at which one is faced with the legal consequences of the basically illegal alcohol-respiration test, based on the relationship between the amount of ingested alcohol and the C_2H_5OH concentration in expired air or in venous blood, a wholly unconstitutional terror, in view of the Rome treaty signed by the Western countries, which says that nobody should be required to cooperate in procedures aimed at providing him guilty. On top of this, the lamentable fact is observable, that among the *professio nobile* there are even those who took the oath of Hippocrates and lend their hands, not to cure (as they promised), but to perform a cubital vein puncture in order to prove someone, who is not their patient, guilty.

The fate of medically active substances within a compartmentalized organism is being unravelled, mainly in the clinical toxicology and pharmacology departments, a laudable, meritorious and necessary effort. Recent years have witnessed such a mushrooming development in this field that today, in many hospitals, in both the emergency wards and outpatient departments of internal medicine, cardiology, neurology, and psychiatry, therapeutic management of the patient would be like a blind date if one did not have the monitoring of intravital drug levels at one's hands.

This book, based on a Boerhaave course on the essence and impact of drug assays, designed and crystallized by our clinical pharmacophilic trio Drs. de Wolff, Mattie, and Breimer, should convince those reading it that therapeutic drug assay does indeed strike a harmonious theme, potentially rich in variations, fully in concert with the ultimate goals of the *dramatis personae*, the patient, physician, and pharmacologist, in question. Pitfalls,

such as physicians' incompetence, patient's non-compliance, and pharmaceutic inefficacy, will be discordantly revealed if the play truly follows its plot.

As a rather old-fashioned doctor, I feel for honesty's sake that I should not keep you unaware of my reserves *vis à vis* any judgement on drug treatment of a patient. This critical attitude was instilled by one of my teachers who, during his ward rounds, used to remark to any suggestion of drug therapy for a patient: "Another colour shoeshine will help him as well." This sophisticated disdain of the pseudo-magic act of prescribing a drug (And who among us do not know from experience many a bitter disappointment?) was translated into a playful persiflage by a recent writer in a deceased journal of which I was one of the editors.

This writer reported the qualities of a panacea called Nietsch®. Its pharmacokinetics adapted themselves miraculously to the species of animals to which it was being experimentally administered prior to clinical trial (fig. 1). Its conversion to ethanol and its other remarkable properties resulting from elimination of N- or Ch-radicals were proposed in dramatic fashion in the *Journal of Phony Results* (fig. 2), an unjustifiably ill-read journal which essentially is a condensation of all articles usually published in pharmaceutic and medical journals. The drug was withdrawn from the market for reasons obscure. An intimation of them however is provided by the curve of the drug's maximal dose effect (fig. 3), which clearly proves that the pharmaceutic

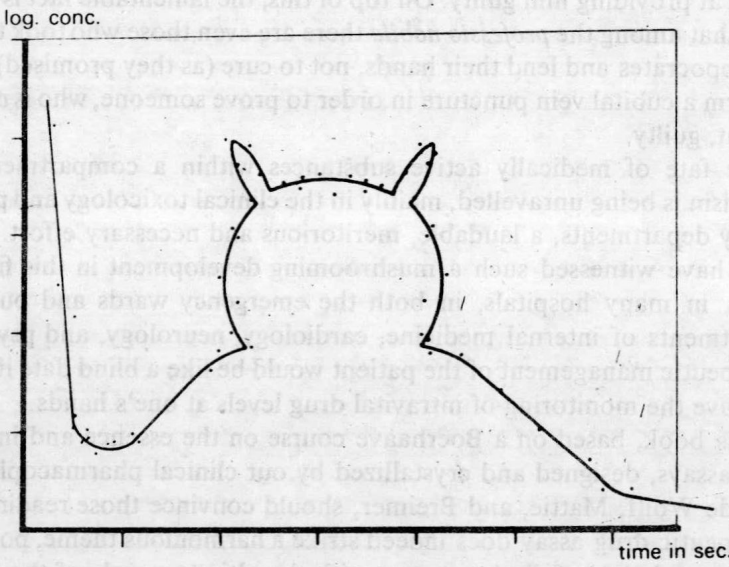

Figure 1. Pharmacokinetics of Nietsch® revealed by experimental administration prior to clinical trial.

competitors must have bought the formula in panic and destroyed it: "Quid rides? Mutato nomine de te fabula narratur!" (Horatius *Saturn* 1, 1, 69).

The experienced physician subscribes to the rationalization (i.e. quantification, reasoning, and logic regulation) of therapeutic measures, allowing

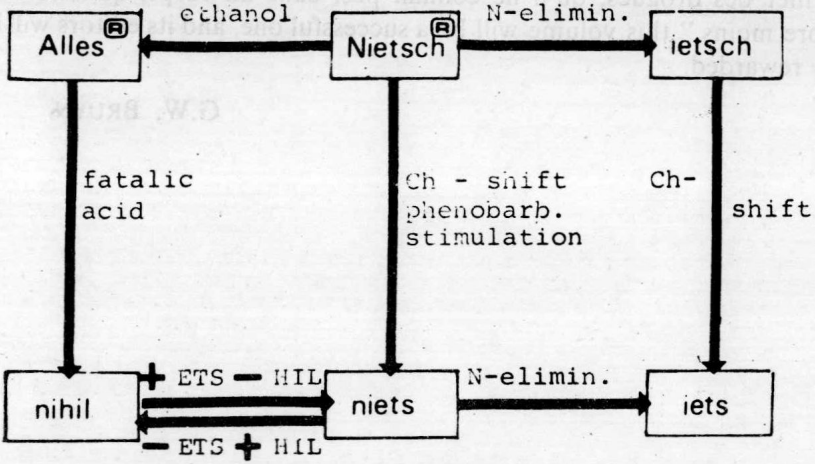

Figure 2. Conversion of Nietsch® to ethanol and its properties resulting from elimination of N- or Ch-radicals. (H.A. Godomski, Pharmacokinetics of the MODEL. *Journal of Phony Results* 1, 1-100, 1978.)

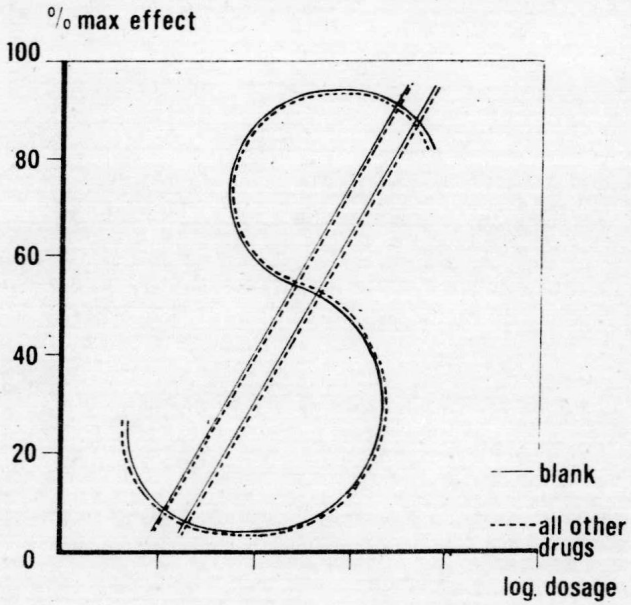

Figure 3. Maximal dose effect of the drug Nietsch.®

for the imponderable factors in the process of cure as yet untouched by the light of scientific progress.

As such, this book is aimed at contributing to augment the rational control of the action of drugs in diseased man. If it materially succeeds in showing today's inapplicability of Voltaire's dictum: "Un médecin est un homme, qui met des drogues, qu'il ne connaît pas, dans un corps, qu'il connaît encore moins," this volume will be a successful one, and its editors will be fully rewarded.

G.W. BRUYN

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PART I GENERAL ASPECTS

1. THERAPEUTIC RELEVANCE OF DRUG ASSAYS

H. MATTIE

There are several reasons why quantities of drugs in body fluids of patients should be determined. Some of these have to do with the individual patient's benefit, some with the advancement of medicine, and of course often both goals are aimed at. Apart from this, the possibility of estimating serum and urinary concentrations of drugs in experiments on healthy volunteers has led to a much better understanding of the biological properties of the pharmaceutic formulation of a drug: whether oral administration is as effective as parenteral administration, what properties good tablets or good suppositories should have, and so on. In this chapter we will limit ourselves to the question of why a doctor should ask for the determination of drugs in a patient.

ESTABLISHING DIAGNOSIS OF DISEASE

First of all, the determination of the presence of drugs in a patient may be a diagnostic procedure. Drugs nowadays are not a rare cause of disease, whether or not they are applied skilfully. Because side effects of drugs are not always exaggerations of the intended therapeutic effect, it is not always unequivocally clear whether a patient has acquired a second disease, or whether he is suffering from the treatment of the initial disease. Even when the side effect is explainable by the drug it is not always dependent upon dose or concentration. This may be explained by some examples. When somebody is drunk, it is assumed that he has had too much alcohol. The diagnosis is often made by observation and common sense on the basis of a few characteristic signs: behaviour and smell, and a history of alcohol consumption. That will suffice in most instances. Nevertheless, even without the possibility of determining alcohol concentrations in blood, it has always been well known that some people can stand much larger quantities of alcohol than others, most often because of adaptation of the central nervous system. Therefore, the question may be asked why alcohol concentrations should be determined when it is known beforehand that a concentration of 1.5 g/l may be consistent with apparently normal behaviour in some people, while a concentration of 0.5 g/l leads to patently abnormal behaviour in others. There are many other examples of diagnostic signs that are equivocal

in the same way: a normal temperature in a patient who is in shock does not exclude severe infection; a normal serum bilirubin does not exclude an obstruction of the biliary duct, at least when it is recent. However, this has never led to abandoning this kind of test altogether. The point to be made is that doctors have learned to work with this kind of data and that they also have to learn the relative importance of serum concentrations of drugs, together with other signs and symptoms, to establish a diagnosis. In the present example: a low alcohol concentration in an experienced drinker, together with grossly abnormal behaviour, will lead to a careful neurological examination, because there might be a serious cerebral lesion. The history alone is insufficient in those cases, because of its known unreliability in heavy drinkers.

GATHERING KNOWLEDGE OF DISEASE

A second good reason for the drug determination is that apart from the useful information obtained from individual patients it may have wider implications. For instance, if alcohol concentrations had not been determined in many otherwise healthy people, or in patients with neurological or endocrine disorders, or in habitual heavy drinkers, we would not have known some important facts, for instance, the fact that habituation to the toxic effect of alcohol in alcoholists is not the result of more rapid metabolism in the liver; or, that acute hepatitis in an alcoholic should not be diagnosed as alcohol hepatitis when there is no alcohol present. Therefore, whenever a doctor thinks of asking for a drug determination, he should ask himself whether he needs it to establish a diagnosis, or to obtain a better insight into the disease in general, as is, or should be, with all diagnostic procedures. The latter indication, the advancement of the knowledge of the disease, is often overlooked. This leads to the erroneous conclusion that if a determination cannot be done immediately it should not be done at all. It may indeed be useless for the patient himself, but the same can be said of an autopsy, and probably nobody will deny the importance of the consistent verification of a diagnosis by pathologic examination. There is, however, a problem that makes drug determinations different from other diagnostic procedures, being that many doctors have not learned to interpret this kind of laboratory finding. For a proper interpretation of a certain drug concentration it is necessary to have some knowledge of the relation between concentration and effect, and of the time relations between administration, concentration and effect. Again this may be illustrated by an example concerning alcohol. The Dutch law allows not more than 0.5 g/l (50 mg/100 ml) of alcohol in the blood for driving. That is not because this is an absolutely safe level, but because of the above-mentioned relations. When blood alcohol

is determined some time after an accident, in most instances the actual level at the time of the accident will have been higher, but how much higher is not easy to tell. It is however possible to make a more accurate guess, by a second determination, some time later, so that the amount of alcohol metabolism in the individual subject may be determined by the difference of the two determinations. The exception is, of course, when the accident took place a very short time after the alcohol ingestion. In this case the alcohol percentage at the time of the test may be *higher* than at the time of the accident, because alcohol was still being absorbed. This does not really excuse the driver, because the mental instability is probably greater with a rapidly rising alcohol level, than with a slowly declining one. This example may illustrate that the maximal diagnostic information can be derived from a drug determination only when all clinical, pharmacological and technical aspects are considered.

Drugs as the cause of disease

In this respect something more should be said about drugs as causes of disease. Some adverse reactions to drugs are more likely to be concentration-dependent than others. When the unwanted effect is an exaggerated pharmacological one it is often concentration-dependent: e.g., extreme sedation by sedatives, deafness by aspirin, bone marrow depression by chloramphenicol. It should be noticed that these are not only exaggerations of the *intended* therapeutic effect, but also well-known pharmacological effects that are unrelated to it. In those instances a drug determination can sometimes establish or confirm the diagnosis or exclude it. Even so the individual sensitivity to a drug at a certain concentration level may vary widely. Sometimes this is firmly established quantitatively, but most often only uncontrolled clinical experience gives us some knowledge of the variation in drug response between individuals. To form this clinical experience it is indeed necessary to collect enough data on the correlation between concentration and effect. In clinical practice every doctor has to decide for himself whether he will rely wholly on data from the literature, or whether he deems it necessary to form his own experience. In this respect it should be mentioned that unfortunately much literature data on the relation between concentration and therapeutic or toxic effect is not so much established facts as opinion.

In general, some toxic effects, for instance those on liver or kidney, tend to be rather closely related to concentration, and more so than many therapeutic effects. One might speculate that this is so, because the therapeutic effects depend a great deal on the state of the disease, which is in itself very variable. Therefore, to avoid toxic concentrations a drug assay is often indicated. A whole class of adverse reactions is not concentration-related, namely the allergic manifestations. Measurement of blood levels in those

instances is quite useless; allergic reactions may even occur after the administration of the drug has already been discontinued, when concentrations are already below the level of detection.

Somewhat in between are some immune phenomena, like the haemolytic anaemia caused by methyldopa. This effect is clearly related to dose and time of exposure, but probably not to the actual concentration at the time this effect is detected. The same hit and run effect can be seen in aspirin thrombopathy: when a patient has a gastric haemorrhage after the use of aspirin, it is more useful to establish his bleeding time than his salicylate level unless one doubts the use of aspirin altogether.

The latter example illustrates an important point, namely that consultation with the laboratory *before* taking samples is often if not always necessary. For the laboratory it often makes a difference whether a qualitative or a quantitative measurement is needed, and whether it is performed on blood or urine. In the above mentioned example this means that a qualitative assay of salicylate in urine may show better whether a patient has taken a salicylate some time before than a serum determination would. In general, drugs that are eliminated mainly in the urine give the clinician the opportunity to assess the total quantity that has been absorbed after ingestion. Of course this can only be done reliably if urine is collected from the moment of admission. Too often the first urine sample is sent to the laboratory for routine tests and then discarded before anybody thinks of its toxicological usefulness.

GUIDANCE OF DRUG THERAPY

A very important reason to determine drug concentrations is for the guidance of drug therapy. Admittedly the need for this is often exaggerated by unexperienced doctors as well as by laboratory specialists, the unexperienced doctor being defined here as the doctor who has not yet learned how to assess the effect of the drug in the patient for whom he prescribed it. For such a doctor, or his patient, a laboratory value is not of much help. As for the laboratory, the supply creates the demand, as is so often the case in clinical medicine. In terms of laboratory organization it is of course more attractive to have a particular drug assay on a routine basis, than to perform it only when really necessary: a car costs less per kilometre the more kilometres driven, but the actual total costs are higher. On the other hand, although one should be warned against the substitution of clinical judgement by drug assays, the undeniable fact that the sensible application of drug assays has enormously contributed to a better treatment of patients should be stressed.

It is important therefore to distinguish between necessary and unneces-