WHAT'S THE DOSE?

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It is doubtful that many in this room would quibble with the statement, in regard to warfarin dosage, that almost every physician appears to behave as if there were no published guidelines for prophylaxis and that he is, so to speak, "therapeutically on his own". What this means in practical terms to individual patients in each of our own communities is that the therapeutic regimen offered depends on which physician is consulted. Moreover, within each category of practitioner, prophylaxis depends on the hospital entered, the service assigned, the specific attending physician responsible for the patient's care, and, at some institutions, the house officer on duty at the time of admission. Private office and clinic outpatient management is no more standardized. In recognition of this absence of consensus it is hoped that several of the presentations to follow may provide some common ground concerning therapeutic regimens that will be of intrinsic value for decision making in cardiac and cerebral vascular disease.

AN HISTORICAL NOTE

The time course of the oral anticoagulant story illustrates the well-known lag phenomenon between discovery of a potential therapeutic agent and the final determination of dose regimens which, in the case of warfarin, is still evolving more than one-half century after the prothrombin time became available. Similar problems exist, of course, for heparin and aspirin both of whose origins date to the 1890's.

Spoiled sweet clover disease was first recognized by the veterinarian Schofield in 1922,1 Paul Link's publications on the synthesis of the coumarin compounds began in 1934,2 and one year later Quick described the methodology of the prothrombin time.3 These seminal observations led to the view that coumarin compounds would have antithrombotic efficacy. That thesis was founded, in fact, upon the observations that the oral anticoagulants produced both a bleeding disease in cattle and a few seconds prolongation of a test tube assay designed to recognize hemophilia. Today, hypotheses based on such evidence alone would be unlikely to reach the stage of clinical trial. Yet, clinical trials in 1941-42 4-6 suggested that the coumarins were effective antithrombotic agents. In short, to quote Peter Medawar: "It doesn't pay to be too clever".7 This is also one example of how investigators have the ability to imagine what the truth might be, before they establish it.
When, however, the results of a large national trial of the efficacy of Dicumarol in acute myocardial infarction was published more than 30 years ago,8 disaffection with the original hypothesis gradually developed.

Moreover, skepticism concerning the efficacy of coumarin drugs in coronary artery disease actually increased as further trials were reported, until the value of oral anticoagulants for any type of thromboembolic episode came into serious question.

The credibility of drug efficacy was damaged not so much by any incompetence among the investigators, but rather by the fact that the scientists of that day were prisoners of the state-of-the-art tools of their trade. These limitations, existing in 1941 and unfortunately to some extent, still present today, include: naivete concerning clinical trial technology, incomplete understanding of the pathophysiology of the disease states being treated, rudimentary information of both normal hemostasis and the process of thrombogenesis, meager insight into the pharmacology and toxicity of the coumarin compounds, and last, but in reality what has been most important to clinicians, inadequate knowledge concerning both the standards required for performing the prothrombin time assay as well as identification of those test values that would provide an antithrombotic effect without producing major bleeding. For dosage was regulated by the prothrombin time which predicted bleeding rather than by assays, animal models or clinical trials that determined the minimal amount of drug required for the desired antithrombotic effect.

Accordingly, the so-called therapeutic range was judged to be somewhat below (but ideally just slightly below) the hemorrhagic level—and the same values were recommended not only for all types of antithrombotic prophylaxis, but for the entire course of the thrombotic process (acute and quiescent) in any individual patient. Under these circumstances, the likelihood of hemorrhage became an overriding deterrent to the widespread use of anticoagulants whose efficacy was under challenge in any event. By analogy, if there had been no blood pressure cuff, and shock had been the endpoint by which the value of antihypertensive therapy had been judged, the current reduction in stroke mortality attributable to antihypertensive medications would never have been achieved.

THE PROTHROMBIN TIME

Growing cynicism toward coumarin compounds was abetted by repeated modifications of the Quick assay. Lack of standardization of the test procedure, particularly as to the nature and reproducibility of the thromboplastin reagent as well as the blood collecting system, led to striking discrepancies in prothrombin times. These disparate results were further compounded by the variety of ways in which the data were expressed for clinical use. Such vagaries led not only to confusion, but to different intensities of treatment. Thus, the same coagulation defect accepted as therapeutic at one institution might be considered homeopathic at another or interpreted as a dangerous overdose at a third.

I believe that it may be through the observations made at this symposium that these physician frustrations in regard to the prothrombin time may at last be put to rest.

But after a standardized prothrombin time becomes available to all, the question will still remain: what's the dose?