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Final remarks

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A. Breckenridge: I would like to reflect with you on what we have achieved over the last 2 1/2 days. Let me say first that we did not set this meeting up to discuss only warfarin. As Gary Levy said to me a couple of nights ago, you could teach the whole of a pharmacology course on warfarin, and I could agree with that. I think we have highlighted several things. Firstly, I think we have shown those areas where there are real gaps in our understanding, and I would exemplify this by Terry Blaschke's talk this afternoon, where he showed quite clearly, the disappointment which he felt that the area of liver disease and optimal drug dosing which has not moved forward since he and several other people were active in the field several years ago. But I think we have identified several positive trends, and I would just like to go through them. From several of the talks, imaging comes over as really a very powerful tool, and that is in spite of Nick Holford's negative comment this morning. It does seem to me that this is showing much promise, and quite clearly, a lot of effort's going into it from industry. Undoubtedly, the most powerful tool remains molecular biology, but we have not yet fully released the value of this discipline in optimising dosing. Further I have learnt, that intensive investigation in certain disease groups pays dividends, and if one looks to what Bill Evans and Mary Relling told us yesterday about how working with relatively inadequate tools, one can, with imaginative application, work wonders in therapeutics, and of course, optimal dosing is part of that. I think most of us are relatively comfortable with the status of our understanding of P450 and PK/PD modelling. Both these have definitely come of age, and I complement Pedro Gambús on his paper, a couple of days ago, showing how PK/PD modelling is being used in that hotbed of clinical pharmacology, the anaesthetic room. That was very impressive. TDM is probably not as important as its proponents would make out. Coming back right to the beginning of the meeting, discussing the pre-clinical to clinical leap, I thought that Kevin Park summarised it beautifully, by saying that each drug must be assessed on its own pharmacological and toxicological merits.

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G. Levy: I cannot let this meeting go by without reminding you of the beneficial role of animal studies. Meindert has already shown examples where the effect of concentration, whether you call it IC_{50} or whatever, of unbound drug in the plasma of animals is often very close to that in humans. Now when Terry spoke about the problems in liver disease, it reminded me of a study that we did that was initiated because of the many reports of falls and hip fractures in people with liver disease who were taking benzodiazepines. We initiated a study using either loss of righting reflex or rotorod performance in rats, and without any problem demonstrated a profound effect of experimental liver disease on the sensitivity to benzodiazepines. In about 15 years of studying the effect of disease on drug action, invariably when there was a well-documented human study, in other words, where protein binding changes were taken into consideration and proper measurements of effect were performed, invariably we could duplicate that in animals. I would suggest that it is highly appropriate in the course of drug development to perform pharmacodynamic animal studies in disease states. I can think of at least a dozen different disease states that can be induced very simply, and in many cases, for example renal failure, one can use different methodologies to produce renal disease in order to exclude the possibility that it is a specific effect due to a particular way of inducing the disease. I just want to go on record here that this is something that can be a very powerful tool. Now I have heard colleagues in industry say "we do not want anything to do with this, because if we do see a disease effect, FDA will make us perform specific studies in people with that disease, and that will hold things up". I suggest that it may often be possible to simply include a statement in the package inserts, saying that animal studies have shown such and such, and while it is not known whether that can be found in humans, nonetheless this will forewarn people, perhaps to start with lower doses or be ready to use higher doses, and be mentally prepared for pharmacodynamic as well as pharmacokinetic changes in a particular disease state.