Clinical Findings

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Conclusions

Final Statements

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Murphy: This is just my own review: A summary of this very elegant symposium is as we have seen in at least two papers. A demonstration that DES and importantly the metabolites of Honvan have direct effects on prostate cancer cells. In the future we are going to have an opportunity to see whether there is synergism potentially with these hormones and other agents:

cyclophosphamide. This will have to be reevaluated in my own limited summary. Honvan is an agent that has had activity. We now must reevaluate it in multicenter and/or multigroup clinical studies. There may be great benefit. This may not be off-set by some toxicity. There are new ways to measure Honvan metabolism. There is evidence that suggests Honvan does have a direct cytotoxic effect experimentally and clinically. It remains to be shown that Honvan is more effective when given by sustained infusion. How much benefit or improvement is unknown presently. To my mind there is no question that this possibility is very high.

Oelschläger: I agree with you, Prof. Murphy, that this satellite symposium was necessary, and I think we have had a full success. From my point of view as an experimental worker, there are three results which have impressed me and two or three things we have to make a strong effort in the near future. The first problem is: We must get a better knowledge of the enzymes involved in the metabolism of Fosfestrol and its metabolites. Now to the question: the nonresponders. We do not know the metabolic pattern of the non-responders. Have they another metabolic scheme? Nobody knows this, but we have to find out. Also there might be a solution of this problem, possibly by the study of metabolic patterns. The third point should be, and that was your idea, we have to look for the maximal doses which will be tolerated by our patients, and we have to accompany these studies by an analysis of all metabolites which will be formed, and we have to do this also quantitatively. Only in this way we will be sure that the answers of these initial experiments are true.

Dunzendorfer: As a clinical urologist I would make some additional conclusions. If you treat with high-dose Fosfestrol, you should never forget to give an adjuvant protective cardiovascular therapy. Secondly, you perhaps should add a therapy as had been mentioned by Dr. Seppelt: low-dose heparin or at least 1 g of aspirin.

It is very important that there is a programmed infusion therapy schedule every 6 to 8 weeks for 10 days or whatever the initiated dose studies will suggest is best. During that time the patient can be infused without entering the hospital, he can take his drug, on an outpatient basis. Furthermore, combination therapy with other cytostatics should be looked at, and there should really be an effort to establish whether these cytostatics effect the bioactivation of Fosfestrol as shown by our research group. If you block the first-pass effect, so that Honvan is

not really cleared by the liver (i.e., if there is another drug that reduces very significantly the bioactivation), then Fosfestrol does not get metabolized and really high doses of diphosphate would circulate for hours. Perhaps at that point clearance in the prostate would even be better. Maybe we must look for a drug that inhibits glucuronidation or sulfatization, for instance, so we really have one drug at a high dose and not all these metabolites, and perhaps then even the nonresponders will respond, because mostly nonresponders may be a problem of a dose relationship.

Heising: For the clinician the most important point I heard today and thought about are the new ways of considering not only drug dosage, but duration of dosage for 24 h, 12 h, and so on. If we review the literature, we see, as in all other carcinoma problems in urology, that most of the studies are not comparable, because they report on different stages, different grades, different dosages, different durations, and so on. For example, the study of Van Erps and Mahler. This study was published in 1984 in *Clinical Trials on Oncology*. I think it is not correct to take a drug, whatever it is, for which for patient use the scientists and clinicians say: The normal dosage is X. You take 40 or 50% of the dosage X, then make a study, and it is published as a final answer. Some of the material of Citrin has also been published in 1985 in *Cancer*. He has presented his study today, and for me it was the most impressive that this modern publication, too, shows the same need for reconsideration of the dosage problem.

Brock: Certainly I will repeat some points of view of my colleagues, but I will start with the first idea of Druckrey which was first an idea, then a hypothesis, and then was supported by experimental and clinical results coming after first existing as a theory. Afterwards there was a great stop in the studies in my opinion, because in the 50's and 60's the methods for biochemical analysis were not available. At any rate, this was the basis, and the new basis is, Prof.

Oelschläger, your and your group's work. From this I believe that we can solve the problem by further study the molecular biological basis of the drug status. For example: What are the decisive metabolites? What are the bioavailabilities of the different metabolites in the target cell? What is the mechanism of action there? I have hope that after the so-called stop we can now make a

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Conclusions

program together with the experts in experimental and clinical fields to solve the problem with success for the patients with prostate cancer. There are many unresolved questions and problems. These problems at present include organotropic toxicity, circulation problems, embolic problems, and so on. Regarding the estrogens and the special compound Stilbestrol, we have shown that with the direct combination – direct efficacy, direct cytotoxic efficacy, and hormonal activity – we have the best compound in our present program. We must make a good plan to solve the other urgent problems step by step. The question is to find out the best dosage over time as regards the therapeutic effect and the toxic effect. It is only useful to increase the therapeutic efficacy, if you have no increase in toxicity. We also have to study and develop, with Dr. Brade's direction, the correct programs, such as the programs in the experimental and in the clinical fields, and bring together experts from both sides. It is not useful today to work separately. If you design a controlled study, it is useful to insert the laboratory of Prof. Oelschläger, so that we can concurrently solve the problems of pharmacodynamics, pharmacokinetics, and of metabolism on a molecular biological basis. I have mentioned the pharmacodynamics. This is a very difficult problem. We need help in this also from the clinical

experiences. If infusion has good results, this will be a very good basis. Then we can work and determine the correct basis from a theoretical point of view. To study the cytotoxic efficacy quantitatively for our compound is a real problem. Regarding the brilliant work of Drs. Schulz and Schneider: What is cytotoxicity, what criteria are there? You can describe it, but quantitatively it is very difficult to identify, and so I have my difficulties to characterize this drug from the point of pharmacodynamics, but we must always keep in mind that that is really a very important factor. Lastly, I am grateful for our common success. I wish to add one word to our friend Dr. Murphy who with his experience over decades has contributed a good part to the success of this day, because both his capacity as moderator and his extensive knowledge have clarified some of the problems which seemed to be not solvable. Dr. Murphy, with your clear spirit, you have shown the right way!

Murphy: The important events of this symposium have been an up-to-date presentation of new scientific data from the laboratory and of pharmacokinetics regarding the activities of Honvan. We have seen unequivocal evidence in human cell lines of prostate cancer cells and in animal models that the drug exerts a direct cytotoxic effect. Moreover

of course

there is evidence

too

that DES does as well. The mechanism of action

as pointed out

will be further elucidated by additional studies. There are

however

important results in terms of the ability to measure the metabolites of Honvan and to know that they exist during conditions such as oral administration and during sustained infusion. It is this latter event which I predict (whether the metabolites are bound to the prostate cancer specifically or nonspecifically) that will foster a relook at the sustained administration of the agent.