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General Discussion

C. R. Hill, J. Mallard, J. Smidt and P. Mansfield

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General discussion

Dr C. R. Hill (*Institute of Cancer Research, Royal Cancer Hospital, Sutton, Surrey, U.K.*). I should like to ask for information and to comment on two topics to which reference has been made during the Meeting.

There is an apparent conflict between the reports that we have been given of the ability of proton n.m.r. measurements to detect malignant change. Professor Damadian and Dr Mansfield claim that this is possible, at least for some advanced cases, whereas Dr Smidt was unable to show significant differences between n.m.r. signals from breast tumours and from non-fatty normal breast tissue. Bearing in mind the desirability of finding an effective means of screening for early cancer, particularly in the breast, it is important to know whether this conflict of evidence is a reflection that the sensitivity of n.m.r. is mainly to the advanced stages of tumour pathology, such as necrosis and cystic degeneration.

My second comment, although a general one, again has particular relevance to the problem of finding a small region of pathology, at an early stage in its differentiation from normality, within a surrounding 'normal' matrix. There is a general theorem that, for any noise-limited imaging system, the linear dimension of an image volume that can be distinguished from a uniform background is inversely proportional to its image contrast against that background. We are starting to see, particularly from the work of Professor Mallard's group, what order of contrast may be available, but none of the authors has given more than in indirect suggestion of the limiting magnitude of the constant of proportionality.

J. Mallard. It is not possible to answer the first question at this stage. We believe that it will be very important to discriminate between proton (water) concentration changes and between T_1 changes. For breast tumours, the T_1 is more than double that from the normal surrounding tissue and we have hopes that this difference may be imaged. In addition, the Yoshida sarcoma implantation study reported in our paper leads to the further hope that the normal tissue responses from the tumour will aid the imaging by making somewhat larger the volume of tissue at an elevated T_1 and, maybe, making it possible to find the tumour earlier.

It is not possible to answer the second question definitely, either, but figure 6 of our paper gives a reasonable attempt to do so at this stage. This figure is concerned with T_1 differentiation only, and does not take into account any proton concentration differences that might exist simultaneously for a given volume of pathology. Also, it is based upon calculation and not on human *in vivo* experimentation.

J. Smidt. I feel that the results that I reported show that one has to be cautious with respect to a more or less general belief that n.m.r. can make a distinction between healthy and malignant tissue as such. Notwithstanding our results, it is, in the case of mamma tissue *in vitro*, still possible to see the abnormal growth of the tumour in the fatty surroundings on account of the different T_{1_1} values of fatty and non-fatty tissue. Early detection of abnormal growth might be of diagnostic value.

P. Mansfield. In replying to Dr Hill's question, there are really two aspects to be considered. The first is that the T_1 results obtained, by Professor Smidt's group, on breast tissue are an attempt to differentiate between the measurements of the breast glandular tissue on the one

hand and the supportive adipose tissue on the other. Their findings confirm that there are large differences between the normal breast glandular tissue and the surrounding fat, as might be expected from the results of many other workers on general T_1 differentiation between adipose tissue, which normally has quite a short T_1, of the order of 100 ms, and other normal body tissues which, generally speaking, have longer T_1's.

The Delft group have also found that malignant mammary glandular tissue has about the same T_1 value as that found in a normal breast. However, in a malignant breast, the abnormal region will, in general, be interpenetrated with the fatty supportive tissue, so that one might expect to see in an n.m.r. imaging experiment a weighted T_1 value that is a composite of the T_1 values for both the fatty and abnormal tissue components. The precise value of this weighted T_1 depends on the degree of interpenetration. It would thus seem that the detection of tumours by n.m.r. imaging depends on the fact that developing tumorous regions increase the T_1 value by virtue of this abnormal ratio of tumour to fat. When we speak of a composite T_1 in this context it is not characteristic of a single relaxation process, since the two regions of the specimen contributing to the overall signal observed relax, in general independently, giving a non-exponential recovery in the so-called slow exchange regime. It is, therefore, not strictly correct to call these composite relaxation times T_1, but effective T_1. However, boundaries and regions in the specimen, where there may be microscopic mixing of the tissues, could well give rise to single relaxation times, and this situation corresponds to the fast exchange regime.

Of course, it has already been established by a number of other workers that some types of tumour do indeed have longer intrinsic spin–lattice relaxation times, and it remains to be seen whether there are intrinsic differences between the different types of breast tumours, malignant or benign.

I do not believe the n.m.r. imaging results of breast tumour detection are a manifestation of advanced stages of tumour pathology, such as necrosis and cystic degeneration, as suggested by Dr Hill. Such advanced stages may themselves be characterized by further intrinsic T_1 changes and are matter for further experimental study. The fact that our results show gradations of T_1, from long values corresponding to what we call the tumour core to shorter values at distances several centimetres away, and the fact that histological examination confirms the presence of malignant tissue penetration over such distances, but in progressively thinner layers and slivers, seems to confirm our belief that we are seeing a T_1 weighting effect. Because the tumour T_1 is so much longer than that of the fatty region, a relatively small interpenetration seems to cause quite substantial changes in the *effective* T_1's observed, producing a kind of amplification effect, which increases their values above the normal fatty tissue background level.

Dr Hills' second question, regarding image contrast, is much more difficult to answer at the present time. As far as I can see, none of the currently proposed imaging methods measures pure n.m.r. parameters, like spin density, T_1, T_2, flow etc., in isolation. Instead, one observes pictures that, depending on the imaging method, variously mix these parameters in subtle ways. For example, in some techniques, very short T_2 regions of a specimen are unobservable, so that one cannot measure either density or T_1. To the extent that T_1 can be isolated, as we have tried to do in our T_1 maps of the breast, for example, it would appear that a greater range of T_1 values can be measured than the corresponding range of water concentrations. As we have demonstrated for most soft tissues, the water content variations (excluding those of bone and bulk body fluids) are about 15 %, centred around the 70 % level. However, the corresponding range of T_1 values spans at least a factor of 10. But in measuring T_1 we must inevitably measure effective water

content, so that the errors in measuring T_1 are correspondingly greater. Indeed, we now believe that edge effects in all imaging schemes currently proposed exacerbate the problem of measuring T_1 accurately. Thus, in practice, the contrast improvements expected by T_1 mapping may not be realizable in currently operational experiments.

It is for this reason that I would hesitate to say, right now, what order of contrast will eventually be available, particularly with reference to Dr Hill's last comment concerning clinically useful images produced in *reasonable* times. For a discussion of imaging times, I refer to my comments in reply to Professor Wilkie's questions (this symposium, p. 531).

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