treatment efficacy so that health economists or other decision makers can decide if the benefit is worth the cost to the community as well as the individual patient.

Consensus conferences are becoming the opium of the physician and they may be a dangerous tool—it would have taken a brave person to bet that between 1900 and 1980 *any* consensus conference would have recommended wide local excision and radiotherapy as the treatment of choice for most women with breast cancer. Our present acceptance of this approach is founded on the results of moderately large trials and it would be an ill day if we allow consensus conferences to replace the need for even larger clinical studies.

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Magnetic Resonance Spectroscopy as a Probe of Tumour Metabolism

As a result of parallel developments in imaging and spectroscopy, nuclear magnetic resonance (NMR) is now extensively used in diagnostic radiology and in biomedical research. Magnetic resonance imaging (MRI), based primarily on the detection of signals from water and fats, has become an established radiological technique, with over 3000 systems currently installed worldwide. Magnetic resonance spectroscopy (MRS) provides a method of studying metabolism, with an emphasis on research applications rather than diagnosis (with one or two notable exceptions that are mentioned below). Here, we are concerned with the possible roles of MRS in oncology.

MRS can be used to prove a wide variety of systems, ranging from body fluids, tissue extracts and cell cultures to non-invasive studies of tissue metabolites in man, which all have a role to play in relation to our understanding of cancer. One of the more controversial topics arose out of the proposal that water-suppressed proton NMR spectroscopy of plasma might provide an approach to the detection of cancer and the monitoring of therapy [1]. This proposal, based on the linewidth properties of the resonances from plasma lipoprotein lipids, has provoked a great deal of further work and correspondence, the strong consensus of opinion being that there are far too many false positives and false negatives for the linewidth measurement to provide a useful test for cancer [2].

It has also been reported that ^{1}H MRS can distinguish between normal and malignant tissue by the detection of neutral lipids in or attached to the membrane protein [3]. On the basis of these and subsequent observations [4], further analysis of this crowded region of the ^{1}H spectrum certainly appears to be justified, but perhaps the emphasis should be not so much on a test for cancer but on understanding in more detail the biochemical abnormalities that are associated with malignant disease. It should be stressed that NMR is not a sensitive technique—relatively high concentrations (typically 0.1–1 mmol/l or greater) are required in order to produce a detectable signal—so that if there is a marker for cancer, techniques that are more sensitive than NMR are likely to be more appropriate.

The prime advantage of MRS is its ability to probe tissue metabolites non-invasively *in vivo*. ^{31}P MRS permits the study of energy metabolism through the signals from ATP, phosphocreatine (PCr) and inorganic phosphate (P_i). Since the frequency of the P_i signal is sensitive to pH, information is available not only about the relative concentrations of these metabolites but also about intracellular pH (the assumption being that most of the P_i is intracellular). In view of the enhanced lactate production that is commonly associated with tumour cells, an interesting observation that has emerged from both animal models and

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human studies is that the intracellular pH measured by NMR tends to be normal or somewhat alkaline [5–9, and references therein]. It should be pointed out that since pH is measured on the basis of the P_i signal, the NMR measurement is weighted towards these regions containing most P_i, so it is conceivable that tumours may contain regions of low P_i concentration which are not reported upon by NMR. Nevertheless, these observations are of relevance not just to the mechanisms whereby tumours control their pH, but also to those treatment regimes which are influenced by whether or not tumour cells are hypoxic.

In animal studies, considerable emphasis has been placed on using ^{31}P MRS to evaluate the response of tumours to therapy [5–7]. There have been two seemingly conflicting patterns of response, one involving an apparent improvement in energy status, with a loss of P_i and increase in PCr, while the other involves a loss of high energy phosphates and a rapid increase in P_i. While the latter can readily be interpreted in terms of rapid cell death, the former pattern was somewhat unexpected. However, it may reflect a complete destruction of some cells (which therefore generate no signal), with a recovery of the energy status of the remainder because of an increase in energy supply relative to energy demand.

These animal studies opened the way to using ^{31}P MRS in clinical studies to evaluate treatment, the overall rationale being that in addition to providing a non-invasive means of monitoring response to therapy, the biochemical changes detected by NMR might precede other signs of response and therefore provide an early guide as to the efficacy of treatment. A number of comments can be made about the current status of this approach.

Firstly, the technology of clinical MRS has been developing over the years; in particular the accuracy of techniques for localising on regions of interest has improved. In addition, just as contrast in MRI can be strongly influenced by variations in the relaxation times T_1 and T_2, so in spectroscopy the relative intensities of the various signals have a relaxation time dependence. Hence caution should be exercised in comparing results from different groups obtained at different stages of technological development and using different pulse sequences. It should be emphasised that skeletal muscle contains a particularly large concentration of PCr, so one always has to beware of the possibility, especially for investigations of limb tumours, that an apparent change in the PCr might reflect a change in the "contaminating" contribution of muscle PCr to the spectrum.

A second point is that the large changes in energy status seen in animal tumours tend not to be seen in human studies. Instead, the focus of attention has shifted towards the phosphomonoester (PME) and phosphodiester signals, which make the other main contributions to the ^{31}P spectrum.

In tumours there is now good evidence that the major contributions to the PME signal are from phosphorylcholine (PC) and phosphorylethanolamine (PE) [6, 7, 10]. Similarly, the phosphodiester region includes contributions from glycerophosphorylcholine (GPC) and glycerophosphorylethanolamine (GPE), but interpretation is not straightforward as mobile lipid components can also generate a large signal in this region of the spectrum [11, 12]. A common characteristic of tumours is an elevation of the PME signal compared with normal tissue, and since PC and PE are intermediates in the pathway of membrane synthesis, this elevation can be interpreted in terms of alterations in membrane metabolism. However, the full biochemical significance of these observations remains to be established. Regardless of the detailed biochemistry underlying these changes, the empirical observation has been made that in human tumours the response to therapy often involves a change in the PME signal, and it is this change which is currently attracting most attention. For example, in serial ^{31}P MRS examinations of a carcinoma of the breast, the changes in the PME signal that were observed during treatment provided a more sensitive indicator of the response to therapy than volume measurements [13].

The third point is that so far there have been relatively few cases in which sequential ^{31}P MRS studies have been reported, so at this stage it is premature to evaluate the eventual role of ^{31}P MRS in the assessment of therapy.

Of the other nuclei that are available for metabolic studies, ^1H and ^{19}F are of particular relevance. As a result of several technical developments, water-suppressed ^1H spectra of very high quality can now be obtained from the brain. Signals of interest include those from N-acetylaspartate and from lactate. Gliomas, for example, show a reduced N-acetylaspartate signal, which is consistent with the belief that this compound is located primarily within neurons, while in some cases the tumour spectra show an elevation in lactate, indicating abnormal glycolytic metabolism [14–17]. Spectra from meningiomas commonly show a relatively intense peak which, with the aid of biopsy studies, can be assigned to alanine [14, 15]. In addition to probing metabolites that are inaccessible to ^{31}P spectroscopy, ^1H MRS has the advantage of relatively high sensitivity, which in turn means that the spatial resolution that can be achieved with ^1H MRS (1–2 cm linear resolution) is superior to that available with ^{31}P MRS (typically 2–5 cm). This helps to overcome the difficulties with spectral interpretation that may arise if, as ^1H MRS has sometimes shown, the metabolic state within the region of interest is heterogeneous. As with ^{31}P spectroscopy, further studies are needed to establish the full clinical utility of the technique. Meanwhile, it is apparent that the combined use of ^1H spectroscopy and positron emission tomography (which can probe glucose metabolism and oxygen utilisation), together with the information available from ^{31}P spectroscopy, can provide important new insights into tumour energy metabolism and its control [16–18].

^{19}F is one of the most sensitive of the NMR nuclei, and provides a method for monitoring fluorinated drugs and anaesthetics both *in vivo* and *in vitro*. To date, attention has focused primarily on non-invasive studies of the pharmacokinetics and metabolism of 5-fluorouracil *in vivo* [19–21]. The main point to emphasise here is that ^{19}F MRS permits the simultaneous measurement *in vivo* of both the administered drug and its metabolites, provided that they are present at sufficiently high concentrations (about 100 μmol/l and above). Further information can be obtained from NMR analysis of body fluids, which allow lower concentrations to be detected [22, 23].

In conclusion, MRS can offer a number of fresh insights into tumour biochemistry and evaluation of therapy. In specialised centres, opportunities are available to correlate the relatively global measures of intracranial tumour pH and metabolism derived from ^{31}P MRS with maps displaying lactate and other metabolites detectable by ^1H MRS. If complementary studies with positron emission tomography can be carried out, further correlations can be made with glucose metabolism and oxygen utilisation. The functional and metabolic maps derived from these studies can be superimposed on the MR images that form part of an integrated imaging/spectroscopy examination. More generally, now that magnetic resonance technology has reached a certain level of maturity, there is a need to undertake multicentre trials, using standardised technical and clinical protocols, in

order to establish the efficacy of magnetic resonance spectroscopy in oncology.

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The Autopsy: Its Role in Oncology

IT APPEARS from the recent literature that in several Western countries for which data are available the autopsy rate in hospitals has been steadily declining during the last few decades. In the US [1] and in Germany [2] the rate is currently below 15%; in the UK only the increase in the coroner's autopsy rate compensated for the hospital rate decline [3]. A variety of causes of this worrisome phenomenon have been taken into consideration. As far as the US in particular is concerned, minimum mandatory autopsy rates are no longer part of the accreditation requirements for hospitals, as they were until 1972 [4]. After the publication of the *Accreditation Manual for Hospitals* of the US in 1971, there was an immediate decline in the autopsy rate below the previously fixed quota rate.

The autopsy is often viewed as a time-consuming exercise whose technique has not changed over almost two centuries, and will hardly ever change, and that cannot expect any benefit from automation or other sophistications except for encoding and data retrieval in the future [5]. Autopsy is also financially unrewarding. The quality of anatomical diagnoses produced by young assistants or young trainees with reference to inaccuracy, lack of documentation or even carelessness [6] and the frequent delay in communication of the anatomical findings have been heavily criticised by clinicians. Also, the usefulness of the autopsy after the introduction of many sophisticated antemortem diagnostic paraphernalia, especially in oncology, has been seriously questioned and this has lowered clinicians' interest and curiosity in unexpected findings—at least in unselected autopsies [7].

Additional negative factors, other than the thanklessness of the task and the apathy of clinicians, are the debatable cost-effectiveness of the whole performance including the postmortem histology assessment [8], the fear of malpractice litigation arising from autopsy findings, medicolegal constraints, the

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