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Editorial Comment

Is research on human tissues at a crossroads?

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The ways in which we diagnose and treat human disease will change dramatically over the next decade, with the development of targeted therapies based on specific biological abnormalities. To achieve the full potential of advances in basic scientific knowledge, there will have to be scientifically-sound translational research, dependent on the availability of large quantities of well-characterised human tissues. This increased need comes at a time when the use of human tissue for research is the subject of much debate. A number of the issues are raised in this issue in a paper by Teodorovic and colleagues [1] which discusses research linked to the tumour bank established by the European Organisation for Research and Treatment of Cancer (EORTC).

Human tissue for research may originate from a number of different sources, including organs donated at autopsy and organs unsuitable for transplantation. However, the most common sources are residual surgical material, blood or body fluids removed in the course of diagnosis or treatment of disease. These have the greatest potential as research tools but are, at present, the source of intense debate. The issues under discussion relate to:

- patient consent
- disclosure of clinical and demographic data that give added value to the material
- mechanisms for collection of tissue
- logistics of storing the tissue resource
- assessment of priorities for the use of stored tissue
- costs.

Historically, residual tissue removed as part of a therapeutic or diagnostic procedure has been regarded as 'abandoned' or 'discarded', and it has often been used in biomedical research without specific patient consent. This is no longer seen as acceptable, and all future use of tissue must be on the basis of informed consent, with the patient 'gifting' tissue. This raises questions regarding how much information the patient needs. Should consent be of a generic or of a specific nature? Currently, there is no uniformity of approach. At one end of the spectrum, there is a body of opinion that the patient must have information on each individual study in which his/her tissue is to be involved, and must give consent for that particular use. This approach is restrictive and may not be welcomed by many patients, as it means that they are contacted on a number of occasions at some time after the original illness. However, it has been adopted in some countries, such as Sweden. With generic consent, the patient agrees to the use of residual tissue in broad categories of research. This is linked to the requirement for projects to be approved on the basis of both scientific and ethical standards by an independent committee before material is released. In general, this is a more acceptable option, but there are still legal and ethical debates over its validity. It is unlikely that the system applied in The Netherlands, where material may be used unless the patient expresses an objection will be adopted widely.

The issue of what is informed consent is worthy of further scrutiny. Clinical trials generally have dedicated staff who can spend time discussing with individual patients the implications of the use of surplus tissues to the benefit of science and healthcare to the 'common good'. This, however, accounts for a very small amount of the surplus tissue that goes through a diagnostic

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pathology department. It is not realistic with the current pressures on healthcare to expect clinicians to spend 20 minutes with each patient explaining the importance of giving permission for use of tissues for research. However, resources are not available to provide dedicated staff for this purpose outside of the setting of clinical trials. As many surveys have demonstrated, the desire of the vast majority of the public is that researchers have access to the surplus tissue and it is the responsibility of the health services to facilitate the desire. What then is the way forward?

The answer must lie in producing a public that is better informed in general on the value of surplus tissues. The introduction of explicit patient/public information sheets for all registrations at hospitals and clinics would be a good start. It would then not be necessary to have a long discussion at a time of stress prior to a procedure, but a clear indication could be recorded of the individual's wishes based on the information previously provided. The ideal position would be for every member of the public to register a choice through a centralised national database.

Obviously, tissues that come with extensive clinical, pathological and life-style information have greater value in most research than those with only a basic diagnosis. The provision of such information raises issues of privacy. There are a number of levels at which specimens can be released to researchers. Anonymised samples have had identifying information removed so that it is not possible for the researcher to identify the individual. Unlinked anonymisation means that no data are stored that would allow anyone to identify the individual. Linked anonymisation means that the researchers cannot identify the individual, but that the information given to the research team will include data that allow specific identification by an independent body—the 'gatekeeper'. Coded samples have an identification that protects confidentiality during use, but the user can break the code and identify the individual. The level of anonymity for any individual specimen will depend primarily on the consent of the individual. Even when full consent has been given, particular studies may use the material at different levels of anonymisation.

Material may be collected in the context of a specific study such as a clinical trial, as in the EORTC bank. This has the advantage of specific focus at the time of collection, but has the disadvantage that there may be only small numbers of samples in any one centre. Provision of tissue for clinical trials impinges significantly on the day-to-day workload of the Pathology Service. Pathologists are under considerable pressure to release blocks for research and the making of tissue arrays by organisations and individuals who do not realise that pathology diagnosis depends on architecture as well as examination of individual cells. This leaves the pathologist with a dilemma. Pathologists wish to support research, but they have an ethical and medico-legal responsibility to ensure that they have adequate material themselves for future assessment of the tumour for review processes and for predictive testing for new drugs that may benefit the patient. Most patients are randomised to trials after surgery and pathological diagnosis. Thus, the pathologist will treat the specimen in a routine way, sampling only sufficient material for diagnostic purposes. It may not always be possible to release such material for research. One solution would be for all centres involved in clinical trials to take an additional 'research block' from all cases. This block would be surplus to the management of the patient and would not be examined by the pathologist. Since it would not be part of the patient record, it could be released for research without medico-legal implications for the pathologist.

It is also important to consider the collection of residual material from as many specimens as possible across one or more institution(s), with the aim of providing tissues for future projects, as yet unspecified. In each of these models, there may be a central bank, or a 'virtual bank', where the tissues are held in a number of centres, but are available to researchers as a single collection. All of these models require significant resource to implement systems that guarantee the quality of the stored material. In addition, the systems must be established with clear lines of accountability and a defined 'trustee'—an individual or an organisation whose role it is 'to protect the rights of individuals and groups and further public interest' [2]. This would serve to reassure individuals that proper use was being made of the tissue they have gifted.

Questions arise as to right of access to the tissue resource, control of release of tissue and judgement of the scientific and ethical aspects of any proposed project. The two main issues are:

- Is the proposed research of sufficient importance to warrant the use of the tissue resource?
- Should there be equality of access to academic or clinical researchers and to the pharmaceutical or biotechnology industries?

All projects, from whatever source, must be reviewed and approved by an appropriate independent Ethics committee or Review Board. Final decisions as to whether material is released for an approved project should be based on scientific assessment of the proposed research. This needs to take into account whether the tissue is in limited supply and how closely the research questions link to healthcare priorities. The culture of research is changing and the line between academia and industry has blurred. It is increasingly recognised that maximum benefit for all can only be achieved through collaboration of healthcare organisations, academia and

the commercial sector. The proportion of research funding contributed by private rather than public funds has increased in most countries. Therefore, tissue resources should be available to all groups of researchers. However, several basic principles apply. Firstly, the patient should give consent for use by these various groups, and any limitations (e.g. refusal of consent for commercial use) respected. Supply of tissue to all groups must be on a cost recovery basis.

There is an issue related to the proposal that the EORTC acquires the intellectual property rights. This does seem to be a sensible way to proceed, but in order for individual hospitals to ensure that the tissue is being used appropriately and under good clinical and research governance, it will necessitate consideration of a Materials Transfer Agreement, between the participating hospitals and the EORTC.

All of these developments necessitate changes in both the healthcare and research communities. They have significant resource implications, in that they require the introduction of new systems that guarantee quality at each step of the process. This will require new approaches by health professionals and managers within healthcare systems to ensure that consent procedures are appropriate and that high quality material is available. It will also change the way in which funding bodies and industry operate, in that much of the cost of tissue provision will have to be seen as an integral part of biomedical research budgets.

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