I I . H U M A N T I S S U E R E S E A R C H

4. The Role and Promise of Human Tissue Research

4.1. Research involving the use of human tissue, or the use of information derived from such human tissue, is a fundamental cornerstone of modern medical research and knowledge. Many of the advances in the life sciences which have contributed so much to our health, physical well-being and long life expectancy are founded on knowledge gleaned in one way or another from human tissue research. For instance, vital epidemiological information about the pattern and incidence of occurrence of various forms of diseases such as cancers has been (and continues to be) gained from human tissue research, and through the analysis of such information, important discoveries about the prevention, control and treatment of such diseases have been made for the benefit of humankind.

4.2. Although tissue banking in some form or another has been practised for well over a century, it is only in the last decade that tissue banking has come into the public limelight because of the rapid advances in research technology and knowledge in the fields of human genetics and genomics. We use the term **"tissue banking"** to refer to a structured and organised resource collection of tissue, put together by one or more individuals for the purposes of facilitating biomedical or genetic research, or for public health and epidemiological purposes, or any combination of these. In the genomics era, research on well-characterised collections of tissues linked with good clinical information, will enormously improve our basic understanding of disease and holds great promise for the discovery of new screening, diagnostic and therapeutic approaches which would benefit mankind.

4.3. However, such research has to take place within a framework which safeguards the public's and patients' interests. In particular, there is a need to ensure that:

a. Tissue is only obtained and collected with the full, free and informed consent of the patient or donor;

b. The taking of tissue does not compromise the patient's clinical care in any way;

c. Where whole organs or whole limbs or substantial parts of either are banked, that these be treated with respect for and sensitivity to religious and cultural perspectives and traditions; and

d. Tissues in tissue banks are used in ethically appropriate ways, and in accordance with the purposes authorised by the consent.

4.4. In this Report, we attempt to canvass some of the issues which we think need to be eventually addressed for the establishment of a sound ethical, legal and social foundation for the proper conduct of human tissue banking and research in Singapore for now and for the future.

5. Human Tissue Banking In Singapore

5.1. **Tissue Collection for Therapeutic or Diagnostic Purposes.** In the past, human tissue banks in Singapore have been built up largely as an incidental by-product of diagnostic procedures. Most commonly, human tissue samples would be removed during surgery or other medical procedures and processed for pathological examination and investigation. For example, suspected tumours would be preserved or fixed in the form of paraffin blocks to facilitate further pathological investigation. These tissue collections largely comprise tissue slides, paraffin blocks and tissue preserved with wet preservation techniques. These techniques render the cellular material non-viable. Some large collections, mostly institutional, have been assembled in this way.

5.2. Pathologists in Singapore have traditionally taken (and continue to take) the view that this retention is on the basis that these tissue samples form part of the medical records of donors, and that they (and the institutional host for the collection) are "stewards and guardians" or custodians of these tissue samples on behalf of the donors.

5.3. Human tissue is collected not only from living donors, but also from the dead. Cadaveric tissue samples are also collected in the course of coronial or consensual autopsies for the purposes of diagnostic procedures.

5.4. On completion of the pathological investigations, these tissue samples (from living and cadaveric donors alike) are generally archived and added to the human tissue collection. The Chapter of Pathologists of the Academy of Medicine, Singapore, states that this is done "in accordance with current good clinical practice guidelines, [so that] the case files (in this case [the] slides and blocks) can be reviewed and perhaps sent for expert opinion. The tissue is kept against the chance that there may be a medico-legal challenge regarding the diagnosis or [in the case of living donors] the possibility that new prognostic and therapeutic markers may be developed, and used during the patient's lifetime".

5.5. Where tissue is collected only for therapeutic or diagnostic purposes (or both), and not for research, the primary objective of the taking of the tissue is the benefit of the patient in the context of the relationship between a physician and patient. In this kind of relationship, the well-established ethical and legal principles and rules governing this professional relationship controls: comprehensive and adequate ethical, professional and legal (both statutory and at common law) controls already exist for the proper governance of this professional relationship, and it is unnecessary for us to add to these in our Report.

5.6. Accordingly, the recommendations set out in this Report are not intended to apply to collections of tissues taken only for therapeutic or diagnostic purposes, and kept only as part of the medical records of patients and not applied towards research purposes (we refer to this kind of tissue collections as **"therapeutic/diagnostic tissue collections"** in this Report).

5.7. **Research Tissue Banks**. However, the status of tissue collections is not always so clear-cut. It is common practice for patients to be asked for their consent to allowing the tissue taken from them for the primary purpose of therapy or diagnosis to be made available for research use after the primary purpose of therapy or diagnosis has been exhausted or satisfied. Consequently, the distinction between therapeutic/diagnostic tissue collections and research tissue collections or research tissue banks becomes blurred, because collections of tissue originally taken for the purpose of therapy or diagnosis eventually effectively become "incidental" tissue banks for research purposes after their original therapeutic or diagnostic purposes are exhausted or satisfied.

5.8. We take the view that if a tissue collection or a tissue bank is made available for research or study (such study being other than for the direct interest and benefit of the donor), then such a tissue collection or tissue bank must be regarded as a **research tissue bank**, regardless of the fact that the tissue may have been originally taken for therapy or diagnosis, or both.

5.9. The main reason for making this distinction between therapeutic/diagnostic tissue collections and research tissue banks is set out at paragraph 5.5 above. In sum, where therapy and diagnosis are the only purposes, the ultimate objectives of both the taking physician and the patient are *ad idem*: the taking of the tissue is aimed at directly benefiting the donor. This is not the case when tissue is taken for research purposes. Research is not aimed at the immediate and direct benefit of the donor, although indirect benefit may accrue to the donor through breakthroughs or advances in medical knowledge or technology as where insights are gained through research involving the use of the donor's tissue. In the

case of the taking of tissue for purely therapeutic or diagnostic reasons, the interests of the taking physician and of the donor patient are in accord: the direct benefit of the patient. In the case of tissue taken for research, this is not the case: researchers necessarily have their own research objectives, and these research objectives are seldom completely coincident with that of direct benefit to the donor individual. For this reason, consent to the taking of tissue for therapy or diagnosis is not consent to the use of the tissue taken for research purposes.

5.10. We are also conscious of the fact that while tissue which is taken purely for therapy or diagnosis is always (and indeed is required by law to be so) taken by registered medical practitioners in the context of the comprehensively regulated ethical, professional and legal relationship between a physician and his patient, there is no guarantee of a similar relationship with its attendant safeguards between a researcher and a donor. Arguably, donors are not covered by this physician-patient relationship even when the research is carried out by registered medical practitioners, because the research is being carried out by the registered medical practitioners in their capacity as researchers, and not in their capacity as physicians to their patient. The ethical, professional and legal safeguards that apply in the physician-patient relationship may have no or limited application in the researcher-donor relationship. That being the case, clear ethical rules and guidelines are required for the ethical conduct of human tissue banking as it relates to research tissue banks, and human tissue research.

5.11. Accordingly, the recommendations set out in this Report are intended to apply to all **research tissue banks**, and to all engaged in the conduct or operation of research tissue banks, regardless of whether therapy or diagnosis was one of the objectives, or was the sole original objective, of the taking of the tissue.

5.12. In recent years, however, research tissue banking in Singapore has moved beyond the merely incidental towards **purpose-assembled research banks**. In this kind of tissue bank, human tissue is collected purely or primarily for the purpose of research, and not merely as an incidental benefit of diagnostic procedures. These purpose-assembled research banks fall squarely within our definition of research tissue banks.

5.13. There has also been a parallel trend towards the establishment of collections of human tissue in which the biological material remains viable or potentially viable, at least in some respects, at the cellular level. For instance, human tissue samples may be flash-frozen and stored in liquid nitrogen or deep freezers. Likewise, cell lines may be propagated on culture media. This greatly increases the value of the samples for many

lines of research, as they can be applied towards a wide range of biological investigations for which fixed materials are not suitable.

5.14. We take the view that such purpose-assembled research banks are to be encouraged, provided that all appropriate ethical and legal considerations and concerns are appropriately met and addressed, as they promote and enhance research, which offers the promise of immense benefit in the future for humankind.

5.15. A significant proportion of current holdings in research tissue banks (as defined by us above) consist of tissues taken originally and primarily for therapeutic or diagnostic purposes. For the purposes of this Report, however, they fall within our definition of research tissue banks notwithstanding the fact that they consist of collections of tissues taken originally and primarily for therapeutic or diagnostic purposes, by reason of their being made accessible or available for research use. The largest collections of these kind of incidental research tissue banks are generally held by hospitals, teaching centres and large health institutions, although some much smaller "private" collections have apparently been built up by individual doctors or groups of doctors in the course of their research into specific medical conditions.

5.16. Our view is that human tissue collections by private individuals should not be encouraged. We therefore propose that, in general, research tissue banks should only be held by institutions (for example, by a hospital, a university or a research institution). Such institutions may be of a public (e.g. a teaching hospital) or private (e.g. a private hospital or a private commercial research venture) character.

5.17. We also take the view that all research tissue banks should be subject to statutory supervision for proper operation, governance and adherence to good practices, compliance with the law, and conduct according to appropriate ethical and professional standards. Given the rapidly evolving state of human tissue research, as well as of the attendant body of ethics both in Singapore and internationally, we think it is best to adopt an approach emphasising professional self-regulation by accredited institutions. This would provide the most flexible and responsive management model in a field which is only in its earliest stage of development in Singapore, and for which field many of the most fundamental issues remain to be settled and agreed upon internationally.

5.18. We therefore suggest that the best and most flexible way of administering such statutory supervision would be to give a statutory authority licensing jurisdiction over all research tissue banks, and that only institutions be licensed to maintain research tissue banks. Through its power to license,

the statutory authority can impose conditions for the issue of licences (such as adherence to and implementation of the principles set out in Recommendation 1 of this Report, and the minimum content suggested by us for the Standard Operating Procedures of research tissue banks in Recommendation 3 of this Report). Such an approach would place the emphasis on institutional responsibility and good internal self-governance, and promote adherence to the spirit of principles rather than to the mere letter of the law.

5.19. We make clear however, that we do not object to the collection of tissue for specific research projects or programs, whether by individuals, or by groups of individuals, provided that the individuals collecting such tissue are employees of or are otherwise directly accountable to an appropriately licensed supervising institution. We appreciate that many research programs which may yield useful and important data and knowledge are assembled by individual researchers or groups of individual researchers in this way. For example, individual researchers or research groups within an university or a medical institution may wish to collect tissue for particular research projects. In such an arrangement, the individual researchers need not be licensed directly by the proposed statutory authority, but may conduct their research under the supervision of a licensed supervising institution and upon such terms as may be stipulated under the general licence granted by the statutory authority to the supervising institution.

5.20. In exceptional cases, if for any reason collections have to be made by private individuals who are not affiliated or directly accountable to any institution (for example, a collection of a specific kind of tissue made by a medical specialist in private practice for the purpose of clinical research in the context of the specialist's own clinical specialty), application should be made by such private individuals to the statutory authority, which may then issue a restricted licence upon such terms as it may deem appropriate. We think that such terms should in particular include an undertaking that the collection, management and use of the tissue collection should only be assembled in collaboration with a licensed supervising institution.

5.21. Institutional human tissue holdings need not be physically centralised. It would be sufficient, for example, for an institution to have in place a current database of all human tissue holdings within that institution. Such a database could be part of the institution's database of research projects, with information fields such as the research area, disease, human tissue collected, where they are stored within the institution, and the units and persons responsible for these human tissues. The database should extend to the tracking of any subdivisions or extracts taken from samples held.

5.22. Consolidation of smaller human tissue collections in larger institutional holdings confers many benefits. A larger institution has more resources for the proper maintenance and stewardship of the human tissue samples under its charge. Continuity and preservation of the human tissue samples are also assured, and there is a greater likelihood of their being available to a wider pool of researchers. By itself, the size of holdings is also an important benefit of consolidation: a large-scale collection is more useful (particularly for population studies) than a small and limited collection.

5.23. We make it clear that in recommending that only institutions be licensed to maintain research tissue banks, we take no position on the issue of ownership, custody and property rights to the tissue in the collection. These are primarily legal questions which remain to be resolved in a definitive way by legislation or the common law. In Recommendation 4 of this Report, we make the recommendation for a continuing professional and public dialogue be initiated towards achieving an early resolution of the legal and ethical questions in relation to ownership, custody and property rights to donated tissues.

5.24. We also recognise that the development of the body of ethics governing research tissue banks and human tissue research is but in its infancy, and that agreement on many of the most fundamental issues have yet to be reached either in Singapore, or domestically within the leading jurisdictions of the world, or internationally. We therefore emphasise that the recommendations contained in this Report should be taken as a contribution towards the development of a mature body of ethics governing human tissue research in Singapore, and not as a definitive end statement of all applicable principles.