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Thoughts on donation of a tooth to science, in the course of dental care

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ABSTRACT
Introduction: Research on biological samples, including dental pulp stem cells (DPSC), has expanded considerably in recent years and is now seen as a way forward toward the possibilities of new therapies, such as craniofacial bone and tooth repair. The extraction of healthy teeth and their donation for scientific research is now well accepted by both patients and researchers alike. The present situation, as described above, presents a timely opportunity to reflect on the ethical and moral obligations of all of the stakeholders involved in this methodology.
Method: Twenty-two patients who received dental treatment between November 2013 and February 2014 in the dental department of Louis Mourier Hospital in Colombes, France, completed a questionnaire. The questionnaire was designed to gather data in respect of giving patients optimal information necessary to acquire informed consent for extraction of teeth to be used for odontological biomedical research.
Results: When patients agree to donate their teeth for purposes of scientific research it is vital that they are properly informed and enabled so that they are able to give consent freely
Conclusions: The risks to patients during dental extractions are minimal. However despite the growing need for a supply of extracted teeth for dental pulp stem cell research it is imperative that any ethical questions that may be raised by potential donors guarantee the security, integrity, and respect of the intentions and aspirations of the donor. To enable the acquisition of true informed consent, this article explores how the dissemination of information relating to biomedical research in the field of dental care must remain as a duty of care and professional ethics.

***KEYWORDS*:** Bioethics; dental pulp stem cells; informed consent; patient rights; biological samples

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INTRODUCTION

Internationally, research on stem cells must meet regulatory guidelines for using human biological material. French law (Article L.1235-2 and L.1245-2 in the Public Health Code) allows surgical residues, collected during surgery, to be used for scientific purposes. This complies with the position shared by the international bioethical community.[1]

Bio-banks thus represent an important resource for determining the causes and mechanisms of many diseases.

The craniofacial area (bone and tooth) is particularly exposed to trauma, congenital malformations or acquired diseases; tissue loss often requires difficult reconstructions and causes aesthetic and functional disabilities that often deeply affect the patient's quality of life. The evidence of cells endowed with stem cell properties in adult dental pulp has prompted research on the development of alternative therapeutic approaches to craniofacial lesions. The properties of the mesenchymal cells derived from dental pulp (or dental pulp stem cells, DPSC) have been shown very similar, although not identical, to those of bone marrow mesenchymal stem cells.[2,3,4,5] Mesenchymal stem cells have now been isolated from many other tissues, potentially interesting for therapeutic use—in particular, the adipose tissue and the umbilical cord blood. However, as DPSC have a neural crest origin,[6] it is conceivable that they might be more efficient in repairing craniofacial lesions than mesenchymal stem cells from a purely mesenchymal origin. In addition, sub-populations of DPSCs also possess adipogenic, chondrogenic, neurogenic, myogenic, and endothelial differentiation capacities *in vitro*,[7] and the capacity of these cells to interact with endothelial cells has been actively studied.[8,9] Several research teams worldwide are presently studying possible new therapies for lesions through tissue engineering using DPSC. This necessitates the frequent collection of human pulp at dental clinics to isolate DPSC for the various, ongoing, experimental programmes. Healthy dental pulp can be easily collected from shedding deciduous teeth or following extraction of deciduous teeth, premolars, or third molars performed as part of an orthodontic treatment plan.

Against this background, the question of knowing how to collect teeth in an ethical manner is posed. On the one hand, the procedure itself is non-invasive way but on the other hand, the patient is in a vulnerable situation during extraction process. To date in most European countries, a tooth extracted in the context of a treatment plan corresponds to clinical waste, and, if used for research, it is considered a biological sample.[10] In this context, this study aims to define the requirements necessary in terms of information and consent to preserve the rights of the donor while ensuring their status as key players engaged in odontological biomedical research.

The research methodology used to compile this article consisted of inviting patients to complete a closed-ended questionnaire and subsequent examination of the outcomes. From this data the article progresses to explore the ethical considerations involved in obtaining the consent of the patient so that their extracted teeth can be used for odontological biomedical research. The feelings of the patient in making this decision are also considered by analysis of specific information provided in the questionnaire that was unrelated to patient protection issues.

MATERIALS AND METHODS

A study involving 22 patients monitored for all-around dental care at Louis Mourier Hospital (Colombes, France) was carried out between November 2013 and February 2014. Twelve questions, prepared in association with the medical ethics laboratory (Table 1), were asked by the

same pollster under specific conditions regarding

- The meaning, donation, and ownership of an extracted tooth
- Information, consent to research after-dental care
- Resulting feedback

This study was carried out to understand the feelings of the patient in respect of their sense of attachment to the tooth designated to be extracted, their understanding in terms of ownership of the tooth (before and after extraction), and their expectations in respect the information provided in order to make informed consent. The study also was also useful in determining the level of trust that existed between patients and their dental surgeon.

Included in the study were French-speaking adult patients, both male and female who were treated in the dental department at Louis Mourier Hospital, Colombes, France between November 2013 and February 2014, and had agreed to take part in a medical experiment. Juvenile, non-French-speaking patients and patients presenting for emergency treatment were not included.

Table 1 - Questionnaire given to patients

Questions	Answers
What does your tooth mean to you?	- Nothing - A part of me - Another answer
Do you consider that your tooth still belongs to you after its extraction?	- Yes - No
Do you look ahead to the possibility of experimentation on your extracted tooth?	- Yes - No
What would you like to do with your tooth after extraction?	- I prefer to keep it - I prefer to leave it - Donate it to science
Would you like to know if any research is conducted on your extracted tooth? If yes, when?	- Yes - No - Consultation before extraction - The day of surgery, just before - After surgery
Would you like the practitioner to ask for your consent to conduct researches on your tooth? If yes, when?	- Yes - No - Before surgery - After surgery
Is there any research that you would not want to be conducted on your tooth?	- Yes - No

Would you like to be informed about the research outcome? If yes, how?	- Yes - No - On the phone - Email - By letter
If you give your tooth to science do you consider that it still belongs to you or that it belongs to the researcher?	- It will always be mine - Il belongs to the researcher
who should inform you about the possibility of donating your tooth to science?	- The surgeon - Other member of the health-care team
Would you be afraid to have your tooth extracted for research instead of medical reasons?	- Yes - No
Do you think that in future (a few months or years) you could change your mind and ask for the end of medical research on your tooth?	- Yes - No

RESULTS

Twenty-two patients were included in this study. It had been determined beforehand that all 22 patients understood all of the questions. Patients were apt to visualize how a research team would use their extracted tooth. The answers of each patient were collated after every interview. From the answers to each question it was possible to quantify the patients into defined sub-groups

Eighty-two percent of the patients wished to be informed if their tooth was to be used for research and were willing to consent. Eighty-nine per cent of this group wished to be informed if their tooth was to be used for research and were willing to consent after the extraction had been carried out. All of the patients declared that they wished to be informed about the odontological biomedical research by the dental surgeon.

The results of the questionnaire are presented in Table 2.

DISCUSSION:

This study was designed to gain insight into the status of ownership of a tooth once it has been removed from the patient by a dental surgeon. It also explores with the meaning of tooth donation and the potential loss of belonging to the donor related to the information provided to make informed consent.

What is the status of the extracted tooth?

For more than a half of the patients in this study a tooth represents a part of them integral in the context of eating, smiling or speaking. Once items or products have been taken from the body, they become "special things".[11] According to Professor Poughon[12], parts detached from a human body keep traces of the personality of the soul that once inhabited the body. As such, the extracted teeth in this study become a detached part of the human body intended for research.

In legal terms in all of the countries studied, extracted teeth are similar to clinical waste in that they have no further use. However, if they are used for research, the status of extracted teeth changes as demonstrated in Table 3. Ethically the tooth remains a detached part of the human body and, as such, deserves respect and dignity because physical traces of the donor, for example, DNA remain present. As such repatriation to the donor is possible.

Table 2 - Results

Questions	Answers	Results
What does your tooth mean to you?	- Nothing - A part of me - Another answer	7 15 0
Do you consider that your tooth still belongs to you after its extraction?	- Yes - No	12 10
Do you look ahead to the possibility of us making experimentations on your extracted tooth?	- Yes - No	13 9
What would you like to do with your tooth after extraction?	- I prefer to keep it - I prefer to leave it - Donate it to science	1 0 21
Would you like to know if any research is conducted on your extracted tooth?	- Yes - No	18 4
If yes, when?	- Consultation before extraction - The day of surgery, just before - After surgery	0 2 16
Would you like the practitioner to ask for your consent to conduct research on your tooth?	- Yes - No	18 4
If yes, when?	- Before surgery - After surgery	2 16
Is there any research that you would not want to be realized on your tooth?	- Yes - No	0 22
Would you like to be informed about the research's outcomes?	- Yes - No	7 15
If yes, how?	- On the phone - Email - By letter	0 6 1
If you give your tooth to science do you consider that it still belongs to you or that it belongs to the researcher?	- It will always be mine - It belongs to the researcher	0 22
Who should inform you about the possibility of donating your tooth to science?	- The surgeon - Other member of the health-care team	22 0
Would you be afraid to have your tooth extracted for research instead of medical reasons?	- Yes - No	0 22
Do you think that in future (a few months or years) you could change your mind and ask for the end of medical research on your tooth?	- Yes - No	0 22

Who owns the extracted tooth?

Barely more than half of the patients considered that the extracted tooth still belonged to them.

In legal terms in some countries, for example, England, there is no law granting right of ownership in respect of the human body, its parts, and products.[13] In France, the civil code reaffirms that the human body, its parts and products cannot be subject to laws of property right. In America in the case of John Moore, the Supreme Court of California held that a patient could not claim right of ownership over human tissue designated for destruction. However, in terms of ethics, the French National Ethics Committee[14] confirmed that the human body, its elements, and its extracts cannot be subject to property rights. The medical or research team is, therefore, only the depository and guardian of biological samples. Against this background the extracted tooth belongs to the patient as long as he or she has not expressed a desire to release it from his or her possession. This ensures that the consent of the person, and source of the tooth, is respected at all times when the tooth is transferred or reused.

The reasons outlined above could probably explain why all the patients interviewed in this study considered that the tooth belonged to the researcher as soon as it was donated to science.

Table 3 - Examples of legal status of extracted teeth

Countries	Legal basis	Extracted tooth not used for research	Extracted tooth used for research
France	CSP Article L.1245-2	Clinical waste	Biological sample
England	Nuffield Council on Bioethics, "Human Tissue: Ethical and Legal Issues", April 1995	Clinical waste	Tissue removed in the course of medical treatment and used for research
Switzerland	Swiss Academy of the Medical Sciences. Biobanks, taking, conservation and use of biologic human sample.	Clinical waste	Surplus of human biological sample used for research
Germany	Nationaler Ethikrat, "Biobanks for research", Notice, 2004	Clinical waste	Human tissue removed for the purposes of treatment and subsequently used for research
Belgium	Law Article 20 of December 19th, 2008 concerns the obtainment and use of human physical samples intended for human medical applications or for scientific research. Bioethics Advisory Committee, Notice N°45 of January 19th, 2009 features the banking of human samples for research.	Clinical waste	` Residual human tissue used for research
Council of Europe	Recommendation (Article 12, 2006) of the Committee of Ministers to EU member states about research involving human biological samples. .	Clinical waste	Residual human tissue used for research

Canada	Tri-council policy statement, "Ethical Conduct in Research involving Humans", 1998	Clinical waste	Tissue already removed in the course of medical treatment and used for research
Singapore	Bioethics Advisory Committee, "Human Tissue Research", 2012	Clinical waste	Human tissue removed for the purposes of treatment and subsequently used for research

Is this a donation?

Following extraction of the tooth, three possibilities were available to the patient for consideration in respect of the future of the extracted tooth: (1) reclamation of the tooth by the patient (2) collection of the tooth by an external party for research purposes (3) No preference by the patient and, in this eventuality, the tooth would be destroyed.

The first possibility is very specific to the tooth because of its symbolism from early childhood. The majority of the patients interviewed agreed to donate the extracted tooth to science, although nine of the twenty two patients had not considered this eventuality before the extraction.

When patients were asked if they wished to keep hold onto the extracted tooth in the absence of any information regarding the ultimate destination of the tooth (incineration or research) and where the patient declined, this was considered as an abandonment of ownership of the extracted tooth by the patient. However, it became apparent that these patients did not envisage that the tooth may have a fate other than incineration. **The refusal of these patients to keep hold onto their extracted teeth does not permit the presumption that they are opposed to research on the cellular component of their extracted teeth.**

In terms of ethics, when a patient was asked if they would consent, or at least if they were not opposed, to their teeth being re-used for purposes of research, then a positive answer to either of these two questions was considered to be a positive response for donation. Patients became aware of the future intentions in respect of the re-use of their teeth and, against this background, any decision was deemed to be truly voluntary.

Criteria for the donation for extracted teeth took on full meaning once patients were empowered with information provided by the dental surgeon that enabled them to make decisions based on freedom of choice. Additionally this survey demonstrated the high level of trust that exists between patient and dentist.

Which information should be given to the patient?

In legal terms in most countries, for example Canada, England, France, and Germany, the information given to the patient must be exhaustive (purpose of the research, duration of the study, risk vs. benefit, etc.). In ethical terms, the broadest possible information ensures the validity of consent.

Only four patients taking part in this study did not wish to be informed about the use of their teeth for purposes of odontological biomedical research. Following extraction these four patients felt that it did not concern them because they perceived that the extracted teeth no longer belonged to them.

However, the majority of the patients taking part in this study expected clear, honest and realistic information in respect

of the future use of their tooth. Most of them expressed the view that they would rather be informed after the tooth had been extracted because it was difficult for them to plan ahead of the extraction. Seven patients wished to be informed "out of curiosity to learn more about the scientific advances in which they would participate". Article 10 of the International Declaration on Human Genetic Data states that "the patient has the right to decide whether to be informed of research results in which he or she has participated.[15] This requirement necessitates the capture and retention of logistical patient details, including names and addresses of patients, and thus precludes patient anonymity. Article 10 of the International Declaration on Human Genetic Data also requires that this information to this effect be recorded in the medical file of the patient.

Who has to inform the patient?

In terms of legality key research personnel in some countries, such as Canada, are responsible for compliance with the consent process.[16] In France, Parliament (Article L.1122-1 of the Public Health Code) has stipulated that either the investigator of the research study or a doctor may transmit equivalent information. From a practical point of view it would be not be unreasonable to expect that the best person to transmit this information to the patient would be the person able to answer all of the potential questions likely to be raised. Against this background a member of the research team would seem to be the most appropriate person.

The Council of Europe does not require that information be provided to participants by a particular person.[17] Information such as this can be given either by the dental surgeon or by another health care team member. In most circumstances the dental surgeon is usually well familiarised with his/her patient and, in this role, is probably best placed to divulge the information. However it may be considered that the dental surgeon is in a sub-optimal position to provide the information in that he/she is not really familiar with ongoing research and, consequently, may not be the best person to properly inform the patient.

Against this background, it is not surprising that one hundred per cent of the patients interviewed in this study declared that they wanted to be informed about the research by their dental surgeon. However it is probable that their dental surgeon may not be privy to and familiar with ongoing specialist research. Consequently they may not be the best person to properly inform the patient.

By introducing a two part process, where the dentist ultimately responsible for the extraction of the tooth is not the same person charged with the obtaining the necessary consent, the patient could be given the opportunity to refuse the extraction without any fear of subsequent reprisal. In these circumstances the consent process could then be seen not to have been be influenced by any perceived patient/practitioner imbalance. Despite this consideration, one hundred per cent of the patients participating in in this study did not consider that their tooth would be extracted for purposes of research rather than for medical reasons. Accordingly there was no conflict of interest between the patient and the dental surgeon who remained independent from the odontological biomedical research.

What features in the consent for tooth donation?

Article 32 of the Declaration of Helsinki, provides for the gathering of informed consent for the use of human tissue for medical research. Article 22 of the Oviedo Convention states the consent is valid only

if the patient is fully informed of the final purpose of the conservation and use of biological elements are removed.

It is therefore necessary to ensure that the patient has not expressed any opposition to the subsequent use of the specimen. Under French law (Article L.1211-2 of the Public Health Code) relevant information must be transmitted to the patient should there be a change in the research programme for which the sample was originally provided.

However it is difficult to imagine how the person from whom a sample was taken could express their compliance to change should there be a change in the research programme for which the sample was originally provided. German[18] and Canadian[16] legislation have established derogation between the information and consent process with the result that it is impossible to contact the person who provided the original biological sample.

One hundred percent of the patients taking part in the study declared that they would not change their mind if asked to take part in a future research project and would not ask for the final results of the project in which their tooth was included. It is significant that all of the patients were aware that any change in the research project for which their tooth was originally intended could possibly result in discovery of genomic and specific information in respect of their present and future health status as well as that of their family. French law (Article L1131-1 of the Public Health Code) stipulates that it is a mandatory requirement to obtain written consent of the patient in cases of genetic research being carried out on the sample provided.

An opinion from the German Ethics Council[18] proposed that consent for the use of any biological sample to be used for research should be "broad brush" and include the possibility of the sample being used for genetic research. Consent would be revocable at any time. This opinion, if exercised, would exclude patient anonymity. Should data become irretrievably dissociated from the human source of the biological sample, sample destruction would be deemed innapropriate[19]. Against this background the introduction of consent for the recovery of surgical residues for research purposes is a matter of concern for some scientists. Nonetheless it does allow for fundamental ethical principles to be respected and could be seen as a means to protect the interests of both the medical and research communities from possible scandal and litigation.

In disputed cases where informed consent is an issue a written signed document is best evidence that the appropriate information was given at the time of consent. However it is recognised that it is more difficult to obtain informed consent than it is to recognise dissent. An expression of consent should be seen as recognition that the patient maintains control over the sample they have provided. By reference to this principle the patient is respected both as a patient and as a human being by virtue of their participation and contribution to a research project contributing to the progress of science[20].

It should be noted that publication of research projects in International Scientific Journals, such as the project described above, require compliance with the rules of ethics, including the dissemination of information and obtaining consent when human body parts are used.[21]

CONCLUSIONS

This study demonstrates that the process of consent for tooth extraction in the context of routine dental care should be separated from that of the extraction of the teeth for purposes of research. The question of the "balance of risk" to the patient associated

with the process of tooth extraction is minimal compared to the potential "greater good" benefits associated with the need of stem cell researchers to have access to dental pulp tissue.[22] The low risk associated with tooth extraction together with the high degree of patient - dentist trust relationship would infer an increased burden of ethical responsibility on the part of the dentist. Currently the dental practitioner is required to safeguard the autonomy of the patient by providing specific information in respect the destination of the tooth for the purposes of research, to obtain informed consent and to establish traceable retrospective pathways in order to reconcile the entire process.

It is suggested that the existence of a continuing climate of mutual trust that currently exists between patients, dentists and researchers will be necessary to ensure that patients will continue to participate in future research projects.

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