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Some Preliminary Questions Concerning Human Cloning

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1. Subject

My intention in this paper is to conduct some preliminary reflections of an essentially factual and linguistic nature which I believe to be lacking in the bioethical literature on human cloning with the result that misunderstandings have arisen from a number of inaccurate preconceptions.

I shall provide a brief description of the cloning technique (Section 1), specify the actors involved and their contributions, and draw up a classification of the possible applications of reproductive human somatic nuclear cloning (Section 2). I shall then analyse a number of technical expressions used in the literature and from which it emerges that reproductive cloning can also be therapeutic (Section 3), and that therapeutic cloning likewise can also (and necessarily) be reproductive (Section 4).

Analysis and clarification of facts and language are indispensable preliminary methodological operations if bioethical issues are to be addressed rationally, and if a semantics is to be constructed which enables the debate to be conducted with the certainty that the same things are being defined with the same words and different things with different words.

2. A Classification of Techniques

Cloning is human reproduction by purely artificial means – that is, without the usual procedure of heterosexual gametic union (neither carnal nor using the *in vitro* technique) involving the fertilization of the female ovum by a fertile male sperm to produce a zygote.

Cloning is an atypical form of reproduction in two respects: it is *asexual* (it does not involve an act of sexual intercourse) and it is *agamic* (there is no fusion of a male and a female gamete). While the former characteristic is nothing new, given that it is common to all artificial reproduction, the latter is of particular interest.

Cloning is a form of artificial reproduction which concerns the creation of a living being which is somatically identical with another genitor living being from which it is derived.

The first necessary distinction with regard to human reproductive cloning is therefore between:

- *Genitor*: the original subject (existing or pre-existing) reproduced in the clone (which comes into existence);¹
- *Clone*: the derived subject which replicates the genitor. Hence, in substance, the clone (newly-existing being) is the somatic copy of an exemplar (and already-existing or previously-existing being).

The scientific significance of the technique used to produce Dolly the sheep, and of its subsequent developments, is that it was able to accomplish the transition from 'cellular' cloning to 'nuclear' cloning. In fact, in scientific terms, a distinction should be drawn between two techniques that fall under the general heading of 'cloning':²

(1) The technique of *embryo splitting* consists in the microsurgical cleavage of an embryo into several derived sub-embryos, thus replicating by artificial means what naturally happens in the case of homozygote twins.³

The technique can only be used to clone from still-undifferentiated embryo cells, or in any case before their fourteenth day of development,⁴ given that totipotency⁵ is inversely proportional to the embryo's stage of development (so

¹ As explained in more detail below, the concept of 'genitor' pertains to the somatic nuclear cloning technique (which is the only one of concrete interest here) and cannot be applied properly to other techniques.

² Not treated here is parthenogenesis, although some authors consider it to be a third cloning technique (cf. Balistreri, 2004, 13 and 24), essentially because it is still a merely experimental technique (which has not yet produced positive results with mammals). By 'parthenogenesis' is meant the production of an embryo by the chemical or electrical stimulation of the egg cell without the use of sperm.

³ 'Homozygote twins' are individuals born from a natural splitting of the embryo. Because they derive from the same gametes (same egg and same spermatozoon), they are genetically identical. A distinction should be drawn between 'homozygote' twins, which are born simultaneously and derive from the splitting of a single zygote, and 'fraternal twins', which instead derive from two or more zygotes although they too are born simultaneously (Sgaramella, 1998, 52).

⁴ By the fourteenth day, the primitive streak (or embryonal line) which enables identification of the cranio-caudal axis and the dorsal and ventral surfaces has appeared. It therefore represents the limit for the formation of multiple embryos (cf. Flamigni, 1998, 53 ff.).

⁵ By 'totipotency' is meant the capacity of a cell to generate a complete organism. This capacity is possessed by the embryo cells from the zygote phase to the morula phase (from conception until the fifth day). By 'pluripotency' is meant the capacity of a cell to generate any type of tissue (that is to say, individual cells are still totipotent as regards the cellular progeny but no longer in epigenetic terms). This capacity is

that as the differentiation process proceeds, the embryo's totipotency diminishes until it disappears⁶), it yields a maximum of two or three copies.⁷

The genitor can therefore only be an embryo in the totipotency phase, with the consequence that the qualities of the offspring cannot be predicted with ease.

In 1993 two American researchers at George Washington University used the embryo splitting technique to divide human embryos *in vitro* in order to examine their duplication. Their experiments, however, were conducted on embryos anomalous in that they were fertilized by two spermatozoa and therefore unable to develop for more than a few days (in fact, the differentiation process yielded a maximum of 32 cells).

(2) The technique of *nuclear transfer* consists in the use of an electrical pulse to fuse a cell nucleus with the denucleated oocyte⁸ of another cell.

The genetic nucleus can be removed from an embryonal, foetal, or somatic cell.⁹ The first case (the embryonic or foetal nucleus can be treated jointly) is that of 'embryonic' or 'foetal' nuclear cloning,¹⁰ which does not greatly differ from embryo splitting as regards predicting the qualities of the progeny (because the point of departure is again an embryo or foetus, i.e. an unborn being). The second case is that of 'somatic nuclear cloning', which enables reproduction of unlimited copies of individual adults (because a genitor can be cloned an unlimited number of times, and at any moment, given that it is only necessary to collect a single somatic cell from it).

It is today possible to equate the *embryonic genome* (the set of the embryo's still-undifferentiated cells) with the *somatic genome* (the set of the adult's by now differentiated cells). The former is totipotent, that is, able to generate one complete organism. The latter is able (at least in some of its components under

possessed by embryo cells from the blastocyst phase (sixth day) onwards. The subsequent phases are those of multipotency and unipotency. By 'multipotency' is meant the capacity of a cell to give rise to a specific range of tissues, and by 'unipotency' its capacity to generate only one type of tissue.

⁶ After the fifth day, the individual cells are no longer epigenetically totipotent (from the blastocyst phase onwards they are pluripotent), although the embryo as a whole retains its epigenetic totipotency until the fourteenth day.

⁷ The number of possible splits is limited because of the cytoplasmic insufficiency of the mammal surrogate mother, which is unable to keep a larger number of sub-embryos alive, and (in the case of several surrogate gestants) because the sub-embryos deriving from the splitting of the initial embryo can be divided only a limited number of times.

⁸ A 'denucleated oocyte' (or 'ooplast') is a oocyte whose nucleus has been removed.

⁹ V. Sgaramella, 1998, 53.

¹⁰ Embryonic or foetal nuclear cloning is also known as 'paracloning' (Cf. Capella, 2002, 20 and 29).

certain conditions) to recover its original totipotency, something that was always believed impossible, and thus confutes the dogma of the irreversibility of the cell differentiation process.

Every cell of the organism contains all the individual's genetic material, and the nucleus of a somatic cell is able to reproduce a complete organism (and therefore recover its original totipotency) if it is extracted from the adult cell and placed in the cytoplasm of a denucleated oocyte which contains signals and growth factors able to trigger embryonic development.¹¹ This is done by inducing a state of cellular quiescence, in the G0 (g-zero phase) of reduced metabolism when the DNA of the somatic nucleus interacts with the cytoplasm of the denucleated oocyte.¹² This is a process that is still being studied in order to learn how to synchronize the cycles of the donor cell (somatic nucleus) and the receiver cell (denucleated oocyte), but especially to identify and control its signals and growth factors.

In the case of somatic nuclear cloning, therefore, the genitor may be a person of any age; indeed, it may even be a deceased person (in fact, somatic cells can be cryoconserved for a long time).¹³ The genitor is therefore a subject whose characteristics are known. The offspring will have the same sex as the nucleus-donating genitor and its copy in both genetic make-up (although see below) and external appearance.¹⁴

The two novel features of nuclear cloning therefore consist in the possibility to clone individual adults (qualitative feature) and in an unlimited number of copies (quantitative).

There do not appear to have been reproductive experiments on humans using the nuclear transfer technique, despite a number of reports that appeared in the mass media during 2001 but which have not been scientifically confirmed.¹⁵

Since the experiment that led to the birth of Dolly the sheep, the term 'cloning' has been used in its simple form without a defining adjective ('nuclear'

¹¹ Cf. Flamigni, 1998, 457 ff.; Neri, 2001, 63; Sabato, 2002, 46.

¹² Cf. Sgaramella, 1998, 61.

¹³ Cf. Balistreri, 2004, 23.

¹⁴ In the case of Dolly the sheep, the somatic nucleus was taken from a sheep of the Finn Dorset breed, with a grey fleece and black muzzle, while selected as the surrogate mother was a Scottish Blackface, with a white fleece and a black muzzle (Kolata, 1998, 252 ff.). The result was that the difference between genitor and offspring was immediately apparent.

¹⁵ Cf. Meis, "Si, ho clonato un bebé e lo farò nascere entro l'anno", in *Stop*, LV-6, 16 February 2001, pp. 16-17; A. Carlucci, "Dr. Jekyll e Mr. Clone", in *L'Espresso*, XLVII-8, 22 February 2001, pp. 40-45. These press stories concerned the operation by a French scientist, Brigitte Boisselier, director of *Clonaid* (www.clonaid.com), founded in 1997 by the French Raelian sect (www.rael.org) in order to furnish human cloning services for reproductive purposes.

or 'cellular') to denote nuclear cloning, and specifically 'somatic' cloning,¹⁶ a technique whose progress represents the potential for the future scientific development of cloning itself.

In the cases of embryo splitting and 'embryonal' nuclear transfer, the genitor with its typical features¹⁷ does not in fact exist because it has never been born.¹⁸ Hence it can be argued that the concept of genitor *strictu sensu* pertains only to 'somatic' nuclear cloning.¹⁹

When alluding to the product of both cloning techniques, in everyday parlance reference is frequently made to 'photocopying individuals' ('exemplars' in the case of animals) in order to refer to their somatic identity.

Yet, in somatic nuclear cloning²⁰ there are two differences between the genitor and the clone (differences which instead do not exist in the case of embryo splitting²¹):

- There is a *biological difference*²² because the clone develops from a nucleus identical to that of the genitor but in a different cytoplasm. Although the DNA is almost entirely contained in the nucleus, a portion – albeit quantitatively minimal – derives from the mitochondria present within the cytoplasm. (so-called 'mtDNA',²³).

¹⁶ The scientific community regards only nuclear transfer to be cloning in the strict sense (cf. Capella, 2002, 16).

¹⁷ An individual that precedes (or has preceded) a being genotypically identical with the clone and can therefore be a term of comparison.

¹⁸ To those who regard the embryo as a human being from the moment of conception, or in the case of nuclear cloning from the moment of the transnucleation of the oocyte, one may say that it has lived only *in vitro* and has never been implanted in a uterus, even less has it been born. In embryo splitting the 'genitor' embryo is divided into two sub-embryo clones. In 'embryo' nuclear transfer the 'genitor' embryo from which the nucleus is taken is destroyed.

¹⁹ A distinction should be drawn between genitor *latu sensu*, where the genetic endowment is replicated, and genitor *strictu sensu*, where an individual's genetic endowment is replicated. In the case of somatic nuclear cloning we may speak of genitor *strictu sensu* (there is an individual as genitor), while in other cases we may speak at most of 'genitor' *latu sensu* (there is only one genome as genitor), placing the term in inverted commas to indicate that it is being used improperly.

²⁰ The problem does not arise with 'embryo' nuclear cloning because the 'genitor' embryo is destroyed.

²¹ But see note 26 below.

²² Account should be taken of the natural somatic similarity of individuals. Two randomly selected human beings are genetically coincident to a 99.90% extent; siblings are 99.95% coincident (cf. Silver, 1998, 283, note 9). Consequently, in the case of cloning, there is an artificial increase in genetic coincidence which amounts at most to 0.10–0.05% (except in particular cases of homozygote twins).

²³ In mammals mitochondrial DNA consists of a double helix circular molecule comprising 16,569 pairs of bases or nucleotides (less than 10^{-5} the size of the nuclear genome). It is inherited in uniparental, non-Mendelian, manner from the mother be-

Given the minimum quantity of DNA present in the mitochondria (especially in proportion to that contained in the cell nucleus²⁴), it might be believed that it is not relevant to the assessment of the biological differences between genitor and clone.

Nevertheless, the importance of mitochondrial DNA should not be underestimated, because from it may derive genetic anomalies that give rise to severe pathologies: for example, Leber hereditary optical neuropathy (LHON), Leigh's syndrome (MILS), Myoclonus epilepsy associated with ragged-red fibres (MARRF), mitochondrial myopathy with lactic acidosis (MELAS), progressive external ophthalmoplegia (PEO), and others.²⁵

Consequently, the fact that the risk of transmission to the offspring of severe genetic pathologies is linked to both nuclear and mitochondrial DNA demonstrates the objective importance of the genetic contribution by the woman supplying the denucleated oocyte.

- There is also a *biographical difference*, in that the clone is born in a different spatio-temporal situation from that of the genitor²⁶ and therefore lives in its own circumstances and conditions of development.

This difference between genitor and clone, moreover, is twofold, because it concerns both the pre-natal and post-natal stages of their lives.

Given that genitor and clone develop in the wombs of different gestants, it is today known that, during the intrauterine period,²⁷ the offspring participates in the gestant's life. Studies on pre-natal sensoriality report that the foetus is a multiperceptive living being²⁸ able to perceive external sounds and noises, to the point that it participates in the mother's mental and emotional processes.²⁹ Hence it follows that human experiential and relational life begins

cause it derives directly from the cytoplasm of the cells of the germinal line, especially from the oocyte, so that the mitochondrial genes derive to the progeny almost exclusively from the mother (cf. *Harrison's ...*, 1999, 2819; *Molecular ...*, 1995, 812 ff.).

²⁴ An idea of the magnitude of the difference is gained from the fact that the nuclear DNA has around 50,000 genes while the mitochondrial nucleus has only 37 (cf. *Molecular ...*, 1995, 815).

²⁵ Cf. Balistreri, 2004, 41.

²⁶ This spatio-temporal difference is not entirely new, in fact, given that it may also arise in the case of embryo splitting *in vitro* with implant of one sub-embryo in the uterus and cryoconservation of the other. However, the time lag between the implanting of the first embryo and the implanting of the second cannot exceed five years, given the degenerative process to which cryoconserved embryos are subject. And in any case this lag is between clones, not between a genitor and its clone.

²⁷ On the intrauterine period as a distinguishing feature between genitor and clone see Sgaramella, 1998, 48; Neri, 2001, 56.

²⁸ Cf. Bellieni, 2000, 14–21.

²⁹ Cf. Fracassi, 1999, 11–16.

in the maternal womb, during the phase of pre-natal development, given that the mother's external experience is (to a certain extent) shared by the offspring as it interacts with the gestant's organism.

Moreover, in the post-natal phase, since 'environmental' conditions inevitably vary over time in relation to the state of places, things, and persons, the clone develops its own social and cultural life-history different from that of the genitor.

Hence, homozygote twins (and likewise clones produced by embryo splitting³⁰) are more similar to each other (because there is neither the above-mentioned cytoplasmic biological difference nor the spatio-temporal lag of non-simultaneity³¹) than are a genitor and its clone, or two nuclear clones,³² or a clone and its sub-clone.³³

3. Human Reproductive Somatic Nuclear Cloning

A number of distinctions should be made with regard to the applicative possibilities of human reproductive somatic nuclear cloning.

The offspring is the result of the sum of two addends. The first is the biological contribution to the constitution of the genetic endowment of the offspring (G for Genetic), where a distinction must be drawn between G¹, the donor of the nucleus (nuclear DNA), and G², the donor of the oocyte (mitochondrial DNA). G¹ may be of male or female gender, while G² must necessarily be of female gender. The second addend concerns performance of the role, this too biological, of the functional gestator (who brings the pregnancy to term: F for Function). The third factor, N, denotes the offspring resulting from the addition of G+F.

³⁰ Note, however, that clones produced by embryo splitting (unlike natural homozygote twins) may be transferred to the uterus simultaneously.

³¹ However, a post-natal spatial difference may arise if the twins (homozygote or produced by embryo splitting) are separated at birth and assigned to different families resident in different places; for example, when the parents separate and each receives custody of one of the twins.

³² Environmental difference does not necessarily exist in this case, because the clones may come into existence simultaneously (same time) and in the same socio-cultural context (same place), although the cytoplasmic biological difference still obtains.

This latter difference is an invariable feature of nuclear clones (given that they are produced individually, one for each transnucleated oocyte), except in the (extreme) case where two nuclei of the same genome are implanted in denucleated oocytes taken from the same female, who is thereafter the gestant.

³³ The case of the clone and its sub-clone (so-called 'sub-cloning') is similar to that of the genitor and its clone, given that, strictly speaking, the clone is the genitor of the sub-clone.

Addenda G and F both make a biological contribution to N. Specifically, whilst G's contribution is genetic, that of F is organic-functional (biophysiological).

The above components can be used to write the general scheme of reproductive addition:

$$G + F = N$$

Diversifying the genetic contributions yields:

$$G^1, G^2 + F = N$$

The number of subjects involved is variable, and the concrete possibilities are numerous. Application of the technique, in fact, may involve (in biological/functional terms) up to a maximum of three subjects simultaneously (but drawing on a set of five different hypothetical subjects), viz:

- 'α', the customer male, the possible donor of the nucleus (male genitor);
- 'β', the customer female, the possible donor of the oocyte (female genitor) and/or oocyte donor and/or gestant (the female may perform all these roles: see sub 1^{BA} below);
- 'γ', the third-party female, donor of the oocyte, and possible gestator;
- 'ζ', the third-party (male or female) donor of the nucleus;
- 'δ', the third-party male or female donor of the nucleus.³⁴

While the factor N, the offspring, is essentially *simple*, the addend G is naturally *complex* because it may involve a twofold genetic contribution³⁵ (one decisive, G¹ donor of the oocyte, the other almost negligible, G² donor of the oocyte), and it may be *variable* because these subjects do not have fixed roles but may exchange them (α, β, γ, δ). However, although addend F is *simple*, it too is *variable*, because the gestational role may be performed by the future social mother (β) or by a surrogate one (γ, ζ).

Hence, distinguishing according to genetic contribution (given that also addend G, although simple, is variable), the concept of human nuclear somatic reproductive cloning comprises the practicability of six different hypotheses.

Moreover, distinguishing further according to biophysiological contribution (because also addend F is simple yet variable), a distinction must be drawn in each of the hypotheses made as to whether the gestator is the same β customer-

³⁴ δ may also coincide with γ or ζ.

³⁵ The genetic input is twofold because it derives from two distinct sources: the nucleus (G¹) and the cytoplasm of the oocyte (G²). However, it may happen that a twofold contribution is made by the same subject (see sub 1^{BA} and 1^{BB} below).

mother or γ the third-party non-donor of the oocyte. This yields a total of fifteen hypotheses with regard to human reproductive somatic nuclear cloning:

- hypothesis sub 1^A: $\alpha, \beta + F = N$ (Omi)
 - hypothesis sub 1^{AA} ($F = \beta$): $\alpha, \beta + \beta = N$ (Omi)
 - hypothesis sub 1^{AB} ($F = \zeta$): $\alpha, \beta + \zeta = N$ (Omi)
- hypothesis sub 1^B: $\beta, \beta + F = N$ (Omp)
 - hypothesis sub 1^{BA} ($F = \beta$): $\beta, \beta + \beta = N$ (Omp)
 - hypothesis sub 1^{BB} ($F = \zeta$): $\beta, \beta + \zeta = N$ (Omp)
- hypothesis sub 2^A: $\alpha, \gamma + F = N$ (EPd)
 - hypothesis sub 2^{AA} ($F = \gamma$): $\alpha, \gamma + \gamma = N$ (EPd)
 - hypothesis sub 2^{AB} ($F = \zeta$): $\alpha, \gamma + \zeta = N$ (EPd)
 - hypothesis sub 2^{AC} ($F = \beta$): $\alpha, \gamma + \beta = N$ (EPd)
- hypothesis sub 2^B: $\beta, \gamma + F = N$ (EPd)
 - hypothesis sub 2^{BA} ($F = \gamma$): $\beta, \gamma + \gamma = N$ (EPd)
 - hypothesis sub 2^{BB} ($F = \zeta$): $\beta, \gamma + \zeta = N$ (EPd)
 - hypothesis sub 2^{BC} ($F = \beta$): $\beta, \gamma + \beta = N$ (EPd)
- hypothesis sub 2^C: $\delta, \beta + F = N$ (EPf)
 - hypothesis sub 2^{CA} ($F = \beta$): $\delta, \beta + \beta = N$ (EPf)
 - hypothesis sub 2^{CB} ($F = \zeta$): $\delta, \beta + \zeta = N$ (EPf)
- hypothesis sub 3: $\delta, \gamma + F = N$ (ET)
 - hypothesis sub 3^A ($F = \gamma$): $\delta, \gamma + \gamma = N$ (ET)
 - hypothesis sub 3^B ($F = \zeta$): $\delta, \gamma + \zeta = N$ (ET)
 - hypothesis sub 3^C ($F = \beta$): $\delta, \gamma + \beta = N$ (ET)

The final abbreviations (in brackets) are for classificatory purposes. They denote: 'Omi', impure monogenetic homologous (because a minimum of maternal mitochondrial DNA remains); 'Omp', pure monogenetic homologous (because the genetic endowment is entirely furnished by the mother – this is the only case of cloning as the exact reproduction of the genitor's genetic endowment); 'EPd', partly heterologous in the weak sense (given the mitochondrial DNA of the third-party donor of the oocyte); 'EPf', partly heterologous in the strong sense; 'ET', total heterologous.

From this it follows that the objections brought against the heterologous form also apply to human reproductive nuclear somatic cloning. But let us examine the matter case by case.

In the hypotheses sub 1^{AA} and sub 1^{BB}, because F is a third-party female (i.e. ζ coincides with F), we have homologous cloning via surrogate maternity with the gestational mother bringing to term.

Consequently, the objections brought against surrogate maternity with the gestational mother bringing to term can be extended by analogy to these types of human cloning.

In the hypotheses sub 2^{AA} and sub 2^{BA} , because F is the donor γ of the oocyte (i.e. γ coincides with F), we have partly heterologous cloning via surrogate maternity with the gestational mother bringing to term.

Consequently, the objections brought against surrogate maternity with the gestational mother bringing to term can be extended by analogy to these types of human cloning.

In the hypotheses sub 2^{AB} and sub 2^{BB} , because F is a third-party woman non-donor of the oocyte (i.e. ζ coincides with F), we have partly heterologous cloning via surrogate maternity with the gestational mother bringing to term.

Consequently, extendable by analogy to these types of human cloning are both the objections against surrogate maternity with the gestational mother bringing to term, and the objections against heterologous fertilization.

Finally, in the hypothesis sub 2^{CB} , it is necessary to distinguish the case in which δ coincides with ζ from the one in which δ differs from ζ . In the former case, we have partially heterologous cloning via surrogate maternity with the gestational mother donating, and in the latter the gestational mother bringing to term.

In these cases too, therefore, extendable by analogy to these types of human cloning are both the objections against surrogate maternity and those brought against heterologous fertilization.

This raises numerous bioethical questions. I agree with Rodolfo Vázquez³⁶ that certain of these issues (for example, determination of family structures different from the traditional one) do not exclusively pertain to cloning, because they concern other techniques of artificial reproduction, and that they should be addressed "independently of cloning". But I do not agree with Vázquez when he implies that ethical-legal debate on cloning may ignore these issues, for although they concern a wider context, they are intrinsically bound up with cloning technique. They are indubitably independent of cloning, but cloning cannot be independent of them, so that any discussion cannot ignore them.

When it is claimed that 'human cloning is right' or 'human cloning is wrong', and reasons are adduced, one may ask whether those advancing the claim are certain (apart from the fact that they should specify that the reference is to reproductive nuclear somatic human cloning) that those reasons are relevant to all possible applications of cloning technique to humans. Are they certain that they apply to the cloning technique under discussion?

³⁶ Vázquez, 2000, 717, note 11.

Conclusion: The foregoing discussion prompts two considerations. First, cloning is not a technique in and of itself; rather, it interrelates significantly with other artificial reproduction techniques (e.g. surrogate motherhood). Second, aside from general objections regarding the concept itself of human cloning as the replication of the already existent (if the genitor is still alive when the clone is born), it seems ill-advised for ethical and/or legal debate to deal with cloning alone; rather, it should consider the various possible applications of cloning technique in their distinctive features, so that different situations are evaluated (and if necessary regulated) in different ways. Or if it is intended to argue that objectively different situations are ethically-legally equivalent, the relative proof should be adduced. There may, in fact, exist a sort of presumption (susceptible to proof to the contrary) that an objective difference corresponds to an ethical difference. The ethical irrelevance of the objective difference instead needs to be proved.

4. 'Reproductive Cloning' versus 'Therapeutic Cloning' – How can the Notion of Therapy be Extended?

I now examine a number of expressions commonly employed in the bioethical debate on human cloning.

In general, from a purposive point of view, a distinction is usually drawn between 'reproductive' human cloning (RHC) and 'therapeutic' human cloning (THC), where by the former is meant a technique used to generate a human being, and by the latter an application designed to remedy specific pathologies in an already-existing human being (using stem cells).

Consequently, reproductive cloning is not therapeutic cloning, or vice versa, in that therapy and reproduction are two distinct situations.

A number of reservations have been expressed with regard to the notion of 'therapeutic' cloning'.³⁷ These, however, concern ethical aspects, whereas my intention here is to restrict discussion to factual considerations relative to the coherence of the language used (and therefore preliminary to evaluative analysis).

³⁷ See in particular Università Cattolica del Sacro Cuore, 1999, 9–15, which raises two objections against the humanistic and healing purpose of cloning:

- the discrepancy between the therapeutic end pursued and the anti-human means of exploiting and destroying another human being in the early stages of development (the embryo) for experimental purposes;
- the depersonalization of the procreative act, given that therapeutic cloning gives a 'degenerate' meaning to human reproduction, which is engendered for medical-experimental-commercial purposes that reduce the parental figure to the mere donor of biological material.

See Pessina (1999, 140), who claims that "human cloning for therapeutic purposes is morally worse than human cloning to produce children".

In particular, I do not intend to defend the adjective 'therapeutic' in reference to reproduced³⁸ (which would require evaluation of the embryo's ethical-legal status). Instead, I shall relate the notion of therapeuticity to the reproducer alone and verify whether this extension of the notion enables it to encompass the reproductive event as well.

That said, I believe that there are grounds for arguing that the distinction between reproductive and therapeutic cloning is less antithetical than is commonly believed – as if the distinction involved an 'either/or' relation between two opposing concepts.³⁹ In effect, the concepts of reproductive and therapeutic cloning are not necessarily antithetical; nor, therefore, are they necessarily alternatives to each other, nor are they in conflict.

If by 'health' is meant the psycho-physical well-being of the human person, which is – in Italy – by now the usual, though not standard,⁴⁰ interpretation given by case law, then reproduction may be beneficial to the health of the woman concerned (not necessarily the expectant mother – see surrogate maternity) and/or of the couple that reproduces. This notion of health is frequently adduced by those who invoke article 32 of the Constitution⁴¹ to assert the legitimacy of artificial reproduction techniques.

Moreover, this 'extended' notion of well-being intended to incorporate the concept of health into the complexity of the human organism (without restricting it to sterile reductionisms) is also widely embraced at the international level.⁴²

³⁸ Some authors (cf. Balistreri, 2004, 35), although they do not dispute the factual circumstance of the destruction of the embryo, propose that the expression 'therapeutic cloning' be preserved, on the grounds that it would be paradoxical to attribute to the embryo in its early stages of development an importance greater than that commonly attributed to the germinal or somatic cells. Here, however, I shall not engage in evaluation of the ethical-legal status of the human embryo.

³⁹ The contrastive use of the expressions 'reproductive cloning' and 'therapeutic cloning' is by now so widespread in the literature that each has acquired its own specific connotations (negative in the former case, positive in the latter). On the emotive force of the expressions see Castignone, 1998, 11 ff.

⁴⁰ Consider in particular the civil-law institute – of case-law origin – termed "biological damage", the compensability of which rests on the provisions of article 32 of the Constitution and art. 2043 of the Civil Code (as ruled by the Court of Cassation) or art. 2059 (following the recent threefold distinction of "non-pecuniary damage" by the Constitutional Court).

⁴¹ Article 1, clause 1 of the Constitution affirms: "The Republic protects health as a fundamental right of the individual and the interest of the collectivity".

⁴² Consider, for example, the Constitution of the World Health Organization, which defines health as "a state of complete physical, mental and social well-being", which is obviously an assertion that concerns not a real situation but an ideal one to be strived for.

Precise definition is now required of the notion of 'therapeuticity' used in such contexts. By 'therapy' is meant action undertaken to produce concrete benefit for a person's health – the latter broadly understood as psycho-physical well-being in the absence of his/her physical functionality. There are two possible ways in which this situation can be brought about:

- (1) achieving the outcome characteristic of a correctly functioning organism;
- (2) restoring functionality to the organism.

Whether A constitutes therapy is a matter of debate, given the considerations usually put forward with regard to the claimed therapeuticity of artificial reproduction techniques, which do not restore functionality to the organism but instead artificially compensate for a permanent natural handicap. However, while there is dispute as to whether a process which substitutes rather than restores the organism's functionality is therapy, there is general agreement on B.

Hypothesis A we may call therapeutic 'in a broad sense' (and discussion continues on how broad that sense is), and B therapeutic 'in a narrow sense' (relative to the core meaning of 'therapy').

It can be argued that a type-A solution cannot be defined therapeutic in cases where a type-B solution is technically feasible. However, in cases where a type-B solution is not technically feasible, then a type-A solution may be definable as therapeutic. This latter would therefore be a subordinate and residual notion of therapeuticity: because functionality cannot be restored to the organism, and an attempt is made at least to eliminate its unpleasant consequences, enabling the individual to obtain the same result that he or she would have with a correctly functioning organism.

Consider, for example, the case of so-called 'idiopathic sterility',⁴³ where because the causes of the woman's and/or couple's inability to reproduce are unknown, it is not possible to undertake therapy to restore functionality. In this case, therefore, the only option is to resort to artificial reproduction.

From this point of view, the boundary line between therapy in the narrow and broad senses is constantly shifting, because it reflects the theoretical and applied progress of science.

Hence, as we shall see, it may be legitimate (assuming both definition A and definition B) to define also cloning for reproductive purposes as 'therapeutic'.

⁴³ 'Idiopathic sterility' is sterility due to unknown causes (it accounts for circa 10% of cases of sterility).

In effect, from the point of view of the reproducer:

- According to definition A, given that a child has been obtained by means of the cloning technique, the woman and the sterile couple have achieved the outcome that they desire.
- According to definition B, given that a child has been obtained by means of the cloning technique, the psychopathology caused by the sterility or infertility of the woman and couple can be considered cured.

In this regard, what is to be stressed is that the relationship between sterility and psychology in the female organism is so intense that psychologically-caused sterility (so-called 'psychogenic sterility'⁴⁴) can be identified, and also - vice versa - psychological suffering caused by sterility.

The concept of therapy thus stands in contrast to that of illness. Under hypothesis A, it is assumed from the outset that sterility⁴⁵ (or infertility⁴⁶) is an illness⁴⁷ (i.e. the inability to conceive a child). Under hypothesis B, it is assumed from the outset that the psychological suffering of the sterile individual and/or couple is an illness (i.e. the suffering caused by the inability to conceive a child).

This latter aspect should be emphasised. Both physical and psychological suffering pertain to illness because they are its manifestations as well as its constitutive elements. Consequently, if the suffering disappears, the therapy can be considered efficacious.

More in general, Italian case law has by now established the concept of 'psychic damage'⁴⁸ - as particularly intense distress caused to a person - and it is also in the process of incorporating the notion of 'existential damage',⁴⁹

⁴⁴ Cf. Fiumanò, 2000, 57 ff.

⁴⁵ By 'sterility' is meant the inability of a couple to conceive a child after a certain period (usually two years) of sexual relations of normal frequency and without the use of contraceptives: cf. Flamigni, 1998, 272 ff. Sterility may be 'primitive' if there have been no previous pregnancies, or 'secondary' if there has been at least one previous pregnancy.

⁴⁶ By 'infertility' is meant the inability to bring a pregnancy to term: cf. Flamigni, 1998, 275.

⁴⁷ Opinions differ as to whether sterility can be considered an illness. For examination of the arguments in favour of the equivalence between them see Flamigni, 1998, 280. For a critique, see Mori, 1995, 31 ff.

⁴⁸ 'Psychic damage' is usually regarded as a sub-category of 'biological damage', given that its status has not yet been firmly established by jurisprudence.

⁴⁹ On 'existential damage' see Corte di Cassazione, sez. I civ., 7 giugno 2000 no. 7713 (in *Il foro italiano*, Rome, CXXVI, 2001, I, coll. 187-204; in G. Cassano, 2002, 267-270) and Corte di Cassazione, sez. lav., 3 luglio 2001 no. 9009 (in *Responsabilità civile e previdenza*, Milan, LXVI, 2001, 1177 summary, 1192-1198 in full; in G. Cassano, 2002, 643-651).

which relates to emotional and psychological alterations in a person's mental state and to their repercussions on his/her everyday existence.⁵⁰

These notions are not considered here in terms of legal liability; it is my intention instead to emphasise the importance now accorded by the law to a person's psychological suffering, even when it is not directly correlated with contemporaneous physical suffering.

Moreover, a diagnosis of idiopathic sterility may give rise to severe depressive illness such that damage is caused to a person's psycho-physical well-being.⁵¹

On these grounds, therefore, the notion of therapy must necessarily take account of the psychopathological state that may arise in the sterile female organism as a result of an unfulfilled desire for maternity.⁵²

Conclusion: Hence, should one wish to use an either/or antithesis with regard to the purposes of cloning, the distinction to be drawn is between 'reproductive' and 'non-reproductive' cloning in the more general sense, regardless of whether the technique (and its effects) is intended to be therapeutic. This also reflects the extent – as stated above – to which the notion of therapeuticity can be applied to reproductive cloning as well, given that the reproductive purpose may coexist with the therapeutic one, in that the denotative range of the term 'therapy' extends to include the reproductive event.

5. 'Reproductive' versus 'Non-reproductive' Cloning – What is the Biological/Temporal Point (of no Return) that Determines the Reproductivity of the Human Nuclear Cloning Process?

I shall now consider whether this new antithesis ('reproductive cloning' versus 'non-reproductive cloning'), although unproblematic from a purposive point of view, does not give rise to difficulties from the factual one.

The notion's legitimacy has been recently recognized by Sezioni Unite della Corte di Cassazione (21 febbraio 2002 no. 2515, in *Giurisprudenza italiana*, Turin, CLIII, 2002, pp. 1270–1273) and the Corte Costituzionale (11 luglio 2003 no. 233, in *Il foro Italiano*, Rome, CXXVIII, 2003, I, coll. 2201–2207), albeit on different grounds.

⁵⁰ Moreover, whereas 'psychic damage' must be medically ascertained and its symptoms evaluated by clinical diagnosis, 'existential damage' is more closely bound up with the sufferer's quality of life, and therefore with changes of a sentimental and affective nature in his/her everyday lifestyle and aspirations.

⁵¹ Cf. Flamigni, 1998, 277: "for a woman it may be the beginning of a drama: for her (and for many other women) the very purpose of her life may consist in pregnancy and childbirth ... the woman will never be the same: her relationships will change with her husband, family and others ... and she will therefore have a life marked by suffering".

⁵² Cf. Vegetti Finzi, 1997, 133: "in certain respects, the influence of the emotions brings the domain of biotechnology close to that of psychotherapy".

Whilst in abstract the intention to engender reproduction obviously cannot coexist with the intention not to do so (they are mutually exclusive), in concrete terms it should be verified whether cloning for non-reproductive purposes may not engender reproduction and thus be at odds with the intention.

The theme of cloning ('therapeutic', which here is termed 'non-reproductive'⁵³ for the reasons given above) is closely bound up with that of stem cells,⁵⁴ which in 2000 was the subject of heated debate in Italy following a document issued by the Pontificia Accademia per la Vita.⁵⁵

Talk has begun, in fact, of a "new Italian way" to cloning which uses only stem cells taken from the adult organism, rather than from the embryo or the foetus.⁵⁶

A preliminary distinction must be drawn between:

- 'embryo' stem cells (abbreviated to E.S.C.), which can be extracted from human tissue in the embryogenetic stage until the blastocysts are forming;
- 'adult' stem cells (abbreviated to A.S.C.), which can be extracted after birth from human tissues such as bone marrow (HSCs), the brain (NSCs), blood from the umbilical cord (P/CB, placental/Cord Blood).

The taking of adult stem cells does not entail the destruction of embryos and therefore eludes the issue of the ethical-legal status of the embryo. However, it does not seem possible to talk of a "new way", given that research on stem cells in the adult organism has been under way for some time; nor of an "Italian way", given that such research is conducted in various countries of the world and that Italy is not among the leader countries in the sector.⁵⁷

The best prospects are held out by embryo stem cells of autologous type, from which it is possible to derive *in vitro* immunologically compatible cell cultures used to repair tissue lesions in the patient. Adult stem cells, in fact, raise a number of significant quantitative and qualitative problems⁵⁸ concerning

⁵³ Some authors have proposed that the term 'cloning' be used only in reference to reproduction and suggested, in the absence of reproduction, "simple 'nucleus transfer', a neutral term without emotive connotations" (cf. Satolli, 2000, 486).

⁵⁴ For a brief survey of current scientific developments with regard to stem cells see Leone-Mancuso, 2001, 91-109.

⁵⁵ Pontificia Accademia per la Vita, *Dichiarazione sulla produzione e sull'uso scientifico e terapeutico delle cellule staminali embrionali umane*, 24 August 2000 (also published in *Bioetica*, Milan, VIII-3, 2000, 489-495). For a critique see Neri, 2000, 479-484.

⁵⁶ This position has been reiterated by Università Cattolica del Sacro Cuore [2000, 1221-1223].

⁵⁷ Cf. Garattini, 2000, 477.

⁵⁸ For that matter, even those who support research on adult stem cells on ethical grounds acknowledge that "it is not yet possible to compare the therapeutic results obtained and obtainable using embryo stem cells and adult stem cells" (cf. Pontificia

their supply (they are difficult to identify and anyway present in very small quantities) and potential (they have low reproductive capacity and are not pluripotent).⁵⁹

Reference to embryo stem cells entails the difficulty of defining the extension of the concept of 'reproductivity', since the reproductivity or otherwise of human nuclear cloning necessarily requires prior specification of the human embryo's ethical-legal status (given that this particular cloning technique involves irreparable damage to the embryo).

Inspection of the literature seems to show that when the expression 'therapeutic cloning' is used, two different meanings are given to the adjective 'therapeutic'.

In some cases it denotes the purpose of the technical application in the concrete case, and this is the purposive value discussed earlier (section 4), showing that – in reality – this purpose cannot be deemed necessarily in conflict with the reproductive purpose. In other cases, by contrast, it seems that the adjective 'therapeutic' is applied to all cloning that does not involve implanting a transnucleated oocyte in a uterus, this being the discriminatory element at factual level,⁶⁰ regardless of the purpose of their cloning. In this case, 'therapeutic' is equivalent to 'non-reproductive', which is the hypothesis that we are now examining.

However, the technique of human nuclear non-reproductive cloning is the same as human nuclear reproductive cloning, the only difference being the interruption of embryogenesis at the blastocyst stage⁶¹ in order to extract the cells of the inner cell mass (the 'embryoblast'). It is then possible to obtain from the embryoblast *in vitro* cultures of autologous embryo stem cells⁶² to be specialized in the direction desired by processes of induced differentiation.⁶³

Accademia per la Vita, *Dichiarazione sulla produzione e sull'uso scientifico e terapeutico delle cellule staminali*, cit.), although a more recent document states: "the choice of this line of research therefore seems both more technically valid and scientifically valid ... than the use of embryo stem cells" (cf. Pontificia Accademia per la Vita, 2001, 137–145).

⁵⁹ On the differing capacities of embryo and adult stem cells see Neri, 2001, 47 ff.; Sabato, 2002, 42 ff.; Neri, 2000, 481 ff.

⁶⁰ Cf. Serra (2001, 557), who contests the alleged therapeuticity of the cloning technique and affirms: "therefore introduced was the expression 'therapeutic cloning' to denote this process and to distinguish it from 'reproductive cloning', which requires implanting of the transnucleated oocyte in the uterus for its development to proceed".

⁶¹ Cf. Sabato, 2002, 132.

⁶² Stem cells are 'autologous' if the embryoblast has been extracted from the development in the blastocyst of a transnucleated oocyte with the nucleus taken from a cell obtained from the same subject on which subsequent therapeutic intervention is to be performed. Stem cells are 'heterologous' if the embryoblast has been extracted from the development in the blastocyst of a transnucleated oocyte with the nucleus taken

This, however, signifies that in factual terms (i.e. if we do not consider the purposive aspect: the intention of the action) there is a phase – from the trans-nucleation of the oocyte to the formation of the blastocyst – during which there is no distinction between ‘reproductive’ and ‘non-reproductive’ cloning (that is, when the techniques and procedures are identical).

In actual fact, there is a difference between non-reproductive human nuclear cloning and reproductive human nuclear cloning only when the embryo produced is implanted in the uterus.

Hence it follows that:

- (1) For those who argue for the uniqueness of the embryogenesis process, and who therefore use the term ‘embryo’ exclusively to denote the phase of development preceding formation of the foetus,⁶⁴ any form of cloning can only be reproductive (if not in intention, at least in fact) when it involves the formation of an embryo.⁶⁵
- (2) Vice versa, for those who accept the notion of ‘pre-embryo’ (the change-point is usually the fourteenth day from formation of the zygote,^{66,67} but there are other opinions), it is possible to differentiate between a reproductive cloning process, where development continues beyond the fourteenth day, and a non-reproductive cloning process, where development is interrupted before the fourteenth day.

On the latter hypothesis, no embryo in the strict sense is produced, for only a ‘pre-embryo’ has been developed and then destroyed.

This distinction consequently serves to mark out within the embryogenesis a zone of anthropological latency which enables a distinction to be made between reproductive and non-reproductive outcomes.

Consequently, according to position A there is no (and there could not be) nuclear cloning that is not reproductive.

Thus, for the proponents of A, it is irrelevant whether the embryo has an original or derived genetic endowment: what matters is that this is nevertheless

from a cell obtained from a subject different from the one on which subsequent therapeutic intervention is to be performed.

⁶³ Cf. Serra, 2001, 562; Colombo-Neri, 2001, 63.

⁶⁴ In Italy, the Catholic Church has taken up a particularly forceful position on the issue. Cf. Congregazione per la dottrina della fede [1987].

⁶⁵ According to Pontificia Accademia per la Vita, *Dichiarazione sulla produzione e sull'uso scientifico e terapeutico delle cellule staminali embrionali umane*, Rome, cit.

⁶⁶ Cf. Department of Health and Social Security [1984].

⁶⁷ In the case of nuclear cloning, if one does not wish to call the transnucleated oocyte a ‘zygote’, the change-point between pre-embryo and embryo is (and could not be otherwise) the date on which the oocyte is transnucleated.

human genetic material, regardless of what its composition may be. Nor does it matter that the embryo is located in cell cultures rather than being implanted in the womb, given that this objection (made against all *in vitro* fertilization) is countered by pointing out that the technique and form of reproduction do not influence the nature of the reproduced entity.⁶⁸

There is still a question to be settled: the nature (non-zygotic?) of the trans-nucleated oocyte. There are those who have argued that the totipotent human material produced by nuclear cloning is something new, something never produced in nature, a sort of extension of the nucleus donor's body,⁶⁹ because it is not a zygotic embryo that results from the fertilization. In fact, "an oocyte reconstituted with the nucleus of a somatic cell cannot be considered a zygote in the standard sense, because it does not derive from the union of two gametes".⁷⁰ This proposal by the 'Dulbecco Commissione' is therefore not a new scientific departure (it pertains, in fact, to the already-discussed technique of nuclear cloning); it is rather a new interpretation.

Now, whilst it is indubitably true that this is not a zygote in the 'standard sense',⁷¹ it is equally true that it is an embryo (and it is defined as such in the bioethical literature⁷²) – as demonstrated by the fact that if it is placed in normal environmental conditions, it begins the embryogenesis process (in exactly the same way as the zygote).

⁶⁸ Cf. Di Pietro-Sgreccia, 1999, 118: "the fact that it has been obtained by cloning does not change its ontological status, even less the moral obligations ... of the individual and society towards it".

⁶⁹ Cf. Satolli, 2000, 487; Sabato, 2002, 134.

⁷⁰ Commissione di studio per l'uso di cellule staminali per finalità terapeutiche [2000]. On the work of the Commissione see Bompiani, 2001a, 101–25; Bompiani, 2001b, 299–340; Galimberti, 2000, 3–6.

⁷¹ The fertilization and nuclear transfer procedures cannot be likened each to the other, because they are substantially different. The 'zygote' is formed following fusion of the pronuclei of the oocyte and the spermatozoon, each of which (being haploid) delivers 23 chromosomes which give rise to a new single-cell entity. Instead, the 'transnucleated oocyte' is formed by transfer of the somatic cell nucleus to a denucleated oocyte, whose nucleus (being diploid) brings all 46 chromosomes with it (cf. Brovedani, 1997, 35; Satolli, 2000, 487; Sabato, 2002, 15). However, despite the diversity of the procedures, in both cases a diploid single-cell embryo is produced.

If the notion of 'zygote' is not tied to gametic fertilization, then the transnucleated oocyte may be considered a zygote, not in the 'standard sense' but *latu sensu*. If instead, as appears to be the case, the notion of 'zygote' is inextricably bound up with fertilization, then the transnucleated oocyte cannot be considered a zygote. Yet it is indubitably an embryo, simply because it engenders the embryonal process. It would be absurd to argue that it is not an embryo that gives rise to embryogenesis. Therefore, the notions of 'zygote' and 'transnucleated oocyte' are species of the genus 'embryo'.

⁷² Cf. Kolata, 1998, 253; Flamigni, 1998, 459; Galli, 2000, 473; Neri, 2001, 61; Sabato, 2002, 14; Balistreri, 2004, 104.

Consequently, it is no longer scientifically correct to assert that conception marks the beginning of human life,⁷³ because a human life may have agamic origin without being conceived. But precisely because the beginning of a human life may ensue from a transnucleated oocyte, rather than from a zygote, the said transnucleated oocyte can only be considered an embryo.⁷⁴

In the view of those who argue for the personal nature of the embryo, obviously, what matters is the intrinsic capacity of the embryo to develop into a complete human being if placed in the conditions in which every human being is placed to be born. This potential is also possessed by the reconstituted oocyte (first denucleated, then transnucleated), which has the same capacity for development as the zygotic embryo⁷⁵ (although the transnucleated oocyte requires, in the absence of the natural process of embryogenesis by the spermatozoon, to be activated by Sr^{2+} ions or electrical pulses⁷⁶).

In contrast to this is the proposal (also put forward by the 'Dulbecco Commissione') of "nucleus transfer for the production of autologous stem cells" (TNSA) without operating through the embryo at any stage of its development, but immediately directing the transnucleated oocyte towards the production of embryo spheres.⁷⁷ This would be a new scientific departure and not merely a new interpretation.

The proposal has aroused the interest of the Pontificia Accademia per la Vita⁷⁸, which, although acknowledging that at present "the TNSA hypothesis does not appear sufficiently corroborated by experimental evidence", has concluded "it cannot be ruled out ... that this innovative way to produce autologous stem cells may prove viable".

Conclusion: When reasoning in terms of 'non-reproductive' (or, more frequently, 'therapeutic') cloning from embryo stem cells, one assumes – given that it is automatically presupposed – a specific point of view on the ethical-legal status of the human embryo. When instead reasoning in terms of 'reproductive' cloning, one does not necessarily assume a specific point of view on the status of the human embryo (one could refer, for example, to an embryo in

⁷³ Cf. Silver, 1998, 45.

⁷⁴ It could perhaps be said (on the basis of their different genesis) that whereas the zygote is a 'gametic' diploid single-cell embryo, because it is produced with the contribution of two gametes, the transnucleated oocyte is an 'agamic' diploid single-cell embryo because it is produced without the contribution of gametes.

⁷⁵ Cf. Balistreri, 2004, 106.

⁷⁶ Cf. Colombo/Neri, 2001, 63.

⁷⁷ Commissione di studio per l'uso di cellule staminali per finalità terapeutiche [2000]: "the reconstituted oocyte may ... be induced to proliferate and channelled towards the formation of embryonic spheres (not blastocysts) whose differentiation can be directed towards specific stipe-cells".

⁷⁸ Pontificia Accademia per la Vita, 2001.

the eighth week of development,⁷⁹ when there is broad consensus that human life has begun), unless one refers specifically to the initial stage of embryogenesis (e.g. the first fourteen days of the embryo's formation). Hence the use of the former expression is indicative of a specific intellectual position, whilst the use of the latter expression is not necessarily so (it depends on the phase of embryo development being referred to).

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⁷⁹ In the eighth week the embryonal period ceases and the foetal period begins. The embryo is approximately 3 cm long and has formed all its essential structures, both internal and external.

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