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PROPOSED APPROACH TO REGULATION OF
CELLULAR AND TISSUE-BASED PRODUCTS

The Food and Drug Administration

February 28, 1997

PROPOSED APPROACH TO REGULATION OF
CELLULAR AND TISSUE-BASED PRODUCTS

[Docket Number 97N-0068]

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PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS

February 28, 1997

EXECUTIVE SUMMARY

The Food and Drug Administration is proposing a new approach to the regulation of human cellular and tissue-based products. Tissues have long been transplanted in medicine for widespread uses-such as skin replacement after severe burns, tendons and ligaments to repair injuries, heart valves to replace defective ones, corneas to restore eyesight, and the use of human semen and implantation of eggs to help infertile couples start a family. In recent years, scientists have developed new techniques, many derived from biotechnology, that enhance and expand the use of human cells and tissues as therapeutic products. These new techniques hold the promise of some day providing therapies for cancer, AIDS, Parkinson's Disease, hemophilia, anemia, diabetes, and other

serious conditions.

The existing FDA approach to the regulation of human cellular and tissue-based products is highly fragmented. The agency has not previously clearly defined criteria for product characterization, sometimes resulting in confusion on the part of both industry and FDA reviewers. The new regulatory framework, as articulated in this document, would provide a unified approach to the regulation of both traditional and new products. The framework clearly specifies criteria for regulation, and would provide for harmonized review of applications by different Centers within the agency. Additionally, the framework would provide only the degree of government oversight necessary to protect the public health. For products with limited public health concerns, the new framework would allow flexibility and innovation without an application review process.

This new framework would provide a tiered approach to cell and tissue regulation. Regulation would focus on three general areas: 1) preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis; 2) preventing improper handling or processing that might contaminate or damage tissues; 3) ensuring that clinical safety and effectiveness is demonstrated for tissues that are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes.

The agency would recommend, but not require, that screening and testing procedures be followed when reproductive tissues are used between sexually intimate partners, and when tissues are transplanted back into the person from whom they were obtained. The agency would require infectious disease screening and testing for cells and tissues transplanted from one person to another (except for reproductive tissues used between sexually intimate partners). The agency would also require that cells and tissues be handled according to procedures designed to prevent contamination and to preserve tissue function and integrity. In general, there would be no agency submissions required regarding infectious disease controls and handling requirements. Thus, most conventional and reproductive tissues would not be subject to premarket approval requirements (The agency would impose no requirements on cells and tissues transplanted within a patient's body in a single surgical procedure.)

Cells and tissues that were manipulated extensively, combined with non-tissue components, or were to be used for other than their normal functions would be regulated as biologics or devices requiring premarket approval by FDA.
Metabolic cells and tissues, unless minimally manipulated and used for their normal function in the person from whom they were obtained or in close blood relatives of that person, also would be regulated as biologics requiring premarket approval by FDA.

The agency would require that all tissue processing facilities

register with the agency, and list their products, via a simple electronic system.
And the agency would require that all labeling and promotion be clear,
accurate, balanced, and non-misleading.

This new system would provide a rational, comprehensive and comprehensible framework under which tissue processors could develop and market their products. It would ensure that innovation and product development in this rapidly growing medical field could proceed unhindered by unnecessary regulation. At the same time, it would provide physicians and patients with the assurance of safety that the public has come to expect from drugs, biologics, medical devices and other medical products overseen by the FDA.

I. INTRODUCTION

The FDA has formulated a comprehensive approach to the regulation of human cellular and tissue-based products. This approach would provide more appropriate oversight for the wide spectrum of cellular and tissue-based products that are now marketed or envisioned for the future. It would maintain or improve protection of the public and increase public confidence in these new technologies, while permitting significant innovation to go forward unfettered by unnecessary regulatory requirements.

The approach does not encompass vascularized organs or minimally-manipulated bone marrow (both of which are regulated by the Health Resources and Services Administration), transfusable blood products (e.g., whole blood, red blood cells, platelets, and plasma), which the agency already comprehensively regulates, or tissues derived from animals. It also does not encompass other tissue-related products, such as products used in the propagation of cells or tissues, or that are secreted by or extracted from cells or tissues (e.g. human milk, collagen, urokinase, cytokines, and growth factors.) Such products often raise different manufacturing, safety, and effectiveness issues, and generally are covered by other rules, regulations, and/or standards.

II. BACKGROUND

The term "tissues" covers a wide range of products used for many medical purposes. In the past, most human tissue used in medicine was comprised of such body components as skin, bone, corneas, and heart valves that were transplanted for replacement purposes, and semen and ova implanted for reproductive purposes. Except for a small number of tissues previously regulated as devices since 1993, FDA's regulation of the conventional tissues used for replacement purposes has focused on preventing the transmission of communicable disease, as authorized by the Public Health Service Act (PHS Act). Three years ago, FDA promulgated interim requirements that such conventional non-reproductive tissues be tested for HIV and hepatitis

and that their donors be screened for risk of infection. FDA has not previously regulated reproductive tissues.

In recent years, scientists have developed innovative methods of manipulating and using human cells and tissues for therapeutic uses. For example, in what is known as somatic cell therapy, scientists are studying the use of human cells that have been manipulated in the laboratory to treat viral infections (including HIV infection), Parkinson's Disease, diabetes, and other diseases and conditions. Other tissue research includes the use of blood from the placental/umbilical cord, to treat diseases or conditions. In general, these forms of cellular and tissue therapy are regulated by FDA as "biologics" under both the PHS Act and the Federal Food, Drug, and Cosmetic Act (FDCA), with premarketing approval requirements.

III. PUBLIC HEALTH AND REGULATORY CONCERNS ASSOCIATED WITH CELLULAR AND TISSUE-BASED PRODUCTS.

Cellular and tissue-based products and their potential uses are too diverse for a single set of regulatory requirements to be appropriate for all. In an effort to develop a comprehensive scheme that would treat like products alike, but that would establish appropriate regulatory distinctions among cellular and tissue-based products in areas where there were differences, the agency identified the principal public health concerns and attendant regulatory issues associated with the use of these products. Stated as questions, these five overarching public health and regulatory concerns are:

A) How can the transmission of communicable disease be prevented?

B) What processing controls are necessary, e.g., to prevent contamination that could result in an unsafe or ineffective product, and to preserve integrity and function so that products will work as they are intended?

C) How can clinical safety and effectiveness be assured?

D) What labeling is necessary, and what kind of promotion is permissible, for proper use of the product?

E) How can the FDA best monitor and communicate with the cell and tissue industry?

With these concerns in mind, the FDA differentiated cells and tissues and their uses by their risk relative to each concern, so as to enable the agency to provide only that level of oversight relevant to each of the individual areas of concern. Thus, under the plan, tissues would be regulated with a tiered approach based on risk and the necessity for FDA review.

IV. PRODUCT FACTORS (TISSUE CHARACTERISTICS AND USES) AFFECTING EACH AREA OF CONCERN - AN OVERVIEW

The agency has identified the following key product factors relating to the above concerns.

A) Direct transmission of communicable disease. The level of public health concern about communicable disease varies depending in substantial part on the following factors: whether the cells or tissues are used in the same person from whom they were obtained (autologous use); whether the cells or tissues are used in a person different from whom they were obtained (allogeneic use); whether they are banked (stored), shipped, or processed in a facility that handles cells and tissues from multiple donors; whether the cells or tissues are minimally, or more-than-minimally, manipulated;
whether the tissue is viable or nonviable; and for reproductive cells or tissue, whether they are obtained from a sexually-intimate partner of the transplant/insemination recipient.

B) Processing concerns. The level of concern relating to processing is dependent on the following factors: whether or not the cells or tissues are more-than-minimally manipulated; whether or not they are used for their normal (homologous) function; whether or not they are combined with non-cell/non-tissue components; and whether or not they are used for metabolic function. As will be discussed below in VI B, Control of Processing, products that are more-than-minimally manipulated, or are used for purposes other than their normal function, or are combined with non-cell/non-tissue components, or are used for metabolic function, generally will be subject to more comprehensive regulation of processing than products not characterized by any of these factors, although some exceptions may apply. (For example, use for metabolic function would not in and of itself lead to more comprehensive processing regulation when the product was used in the person from whom it was obtained, or in a close blood relative of that person; use of minimally manipulated tissue for other than its normal function may lead to only limited additional regulation of processing, as appropriate to help ensure intended function). Products not characterized by any of these factors would be regulated under section 361 of the PHS Act, and would not be subject to premarketing requirements. Products characterized by one or more of these factors would be regulated under section 351 of the PHS Act and/or under the FDCA, and generally would be subject to some level of premarketing requirements.

C) Clinical safety and effectiveness concerns. Clinical safety and effectiveness concerns depend on the same factors as do processing concerns (i.e., extent of manipulation; homologous or non-homologous function (that is, whether or not tissue is used for its normal function); combination with non-cell/non-tissue components; and metabolic function). The kinds of information the agency will need to address these concerns may differ depending on whether the cellular or tissue-based product is to be used for a local structural purpose (i.e., reconstruction or repair), a reproductive purpose, or a metabolic purpose. As noted above for processing concerns, and as will be discussed below in section VI C, Clinical Safety and Effectiveness, products that are more-than-minimally manipulated, or are used for non-homologous function, or are combined with non-cell/non-tissue

components, or are used for metabolic function, will generally be subject to more comprehensive regulatory controls than products without any of these factors. However, for some products subject to regulation under section 351 and/or the FDCA (see section VI, A, Stem Cells) the agency anticipates establishing product-class-specific processing controls and product standards based on data demonstrating that such controls or standards ensure safety and effectiveness. For these products, applicants would be eligible to certify that these controls and standards have been met in lieu of submitting the underlying data to support such controls and standards.

D) and E) Promotion and labeling and the agency's baseline knowledge of industry are cross-cutting issues that apply to all cellular and tissue-based products, with the exception of cells and tissues obtained from and transplanted back into the same person during a single surgical procedure.

V. THE REGULATORY SCHEME: PRODUCT CONCERNS, PRODUCT CHARACTERISTICS AND USES, REQUIRED INDUSTRY ACTIONS, AND REQUIRED REGULATORY SUBMISSIONS.

The agency has developed a chart (Table 1) that outlines the five principal areas of public health or regulatory concern (rows A through E, as described below), the product factors that affect those concerns (and that are the basis for the subdivisions within rows A, B, and C), the industry actions that would be required to address each set of concerns, and the types of required notifications or submissions to the agency. Thus, to determine all the regulatory mechanisms that would apply to any particular product or use, one must look at all the items in the table. The table is provided only as a very short summary of the regulatory approach. As such, it is not intended to stand alone, but to be referred to in conjunction with this document. The following text elaborates on the issues as presented by row in Table 1.

A) Direct transmission of communicable disease - donor screening, donor/product testing.

1) Overview.
Transmission of communicable disease is a concern for all uses of all cellular or tissue-based products. However, the degree of risk, and the appropriate measures to control risk, vary with the source and use of the product. FDA intends to adjust its regulatory approach accordingly.

Row A of Table 1 broadly distinguishes between cellular and tissue-based products for which the agency would not require communicable-disease controls (A1), and products for which it would require communicable-disease controls (A2). A2 is further subdivided according to the kinds of requirements and tests the agency would consider appropriate, based on the source, use, and characteristics of the tissue. Proposals for specific screening, testing, and related requirements for products in these categories are provided in Table 2.

2) Regulatory requirements.
a) Row A1. The agency would not assert any regulatory control over cells or tissues that are removed from a patient and transplanted back into that patient during a single surgical procedure. The communicable disease risks, as well as safety and effectiveness risks, would generally be no different from those typically associated with surgery. Regulated products used in such procedures would continue to be regulated.

b) Row A2. The use of allogeneic rather than autologous cellular or tissue-based products increases the risk of transmission of communicable disease, because the donor from whom the cells or tissue was obtained could carry an infectious agent to which the recipient is susceptible. Also, for both autologous and allogeneic settings, the use of cellular or tissue-based products that are banked, transported, or processed in facilities with other cellular or tissue-based products increases the risk of transmission of communicable disease, because the products are susceptible to contamination or mix-up at each step of such procedures. For example, an infected product could cross-contaminate other cellular or tissue-based products stored in the same liquid nitrogen freezer, or could contaminate processing equipment, which, if not properly treated, could contaminate other tissue processed with that equipment. If contaminated tissue is not properly tested or labeled, health care workers as well as patients may be put at risk.

Therefore, as shown in rows A2b and A2c of Table 1 and in Table 2, the agency intends to require establishments and persons that bank, ship, or process cells or tissues for allogeneic use (except reproductive tissues from sexually intimate partners of the intended recipient of the tissue) to follow specific donor screening and/or donor or product testing and/or product quarantine procedures. Test requirements will differ depending on whether the cells or tissues are nonviable (A2b) or viable (A2c). Viable cells and tissues that are rich in leukocytes (such as stem cells) can harbor human T-cell lymphotropic virus (HTLV) and cytomegalovirus (CMV), and thus would be required to be tested for those viruses. Viable tissues that are not rich in leukocytes (such as corneas and skin), and nonviable tissues (which do not contain viable leukocytes) would not be subject to HTLV and CMV testing requirements.

In general, the screening and testing would be required to be completed prior to final release of the cells or tissue for transplantation. The establishment or person responsible for determining suitability of release of cells or tissues would be responsible for ensuring that required screening and testing had been performed prior to final release of the material. For cells or tissue to be obtained from a living donor for allogeneic use, screening and testing would be required prior to collection of the cells or tissue (except in extenuating circumstances).

Additionally, as shown in row A2a of Table 1 and in Table 2, the agency intends to recommend (but not require) that establishments and persons that bank, ship or process cells or tissues from multiple donors for autologous use, or reproductive cells or tissues for reproductive use obtained from sexually intimate partners of the intended

recipients of the cells or tissues, also follow the screening and testing procedures prior to collecting the cells or tissue. The agency intends to require that such establishments and persons keep records and label their products as to whether or not recommended donor screening and testing was performed, and if performed, the results obtained. Untested products would be labeled as "untested for BIOHAZARDS."

The screening and testing procedures would be recommended rather than required for such autologous or reproductive uses because 1) autologous use of cells and tissues raises lesser communicable-disease concerns than does allogeneic use; and 2) use of reproductive tissues from sexually intimate partners of intended recipients raises lesser communicable-disease concerns than other allogeneic uses of tissues because the recipient generally will have had prior exposure to the potential risk of receiving communicable disease from that partner. (In contrast, cells or tissue from family-related donors raise the same communicable-disease risks as do cells or tissue from unrelated donors, and consequently family-related donors would be subject to the same testing and screening procedures as are unrelated donors. However, the agency believes that it is appropriate to leave it up to the family and their physician to decide whether to use such tissue, and would not prohibit use even of contaminated material from closely-related donors.)

Cells or tissue from donors who test positive for an infectious disease agent or who have positive risk factors (that is, whose behavior or experiences could have exposed them to infection) would be required to be labeled "BIOHAZARD" or "UNTESTED FOR BIOHAZARD" as applicable, and could only be used for transplantation with the documented advance informed consent of the recipient. Autologous tissue from such donors would be required to be labeled "FOR AUTOLOGOUS USE ONLY". In those situations in which cells or tissues from such donors are not destroyed, the material could be released from a bank or quarantine only upon documented concurrence of the recipient's physician. Such situations would include cells or tissue to be used in the person from whom it was obtained or in a close blood relative (e.g., autologous stem cells); and reproductive tissue for reproductive use (e.g., semen) from a sexually intimate partner of the intended recipient or from a directed donor; medically necessary and otherwise unavailable cells or tissue (e.g., the tissue is a rare histocompatibility match in a setting where matching is critical).

The agency would engage in rulemaking under section 361 of the PHS Act to establish procedures and standards for cellular and tissue-based products not subject to premarket requirements under the PHS Act or the FDCA. While under the section 361 rule there would be no required premarketing submissions to the agency concerning communicable-disease testing, the agency would have authority to inspect facilities subject to the requirements, and to take actions to prevent transmission of communicable disease (e.g., orders of retention, recall, and destruction of cellular and tissue-based products).

Cellular and tissue-based products subject to premarket requirements because of processing or clinical attributes (see sections V B and V C

below) would still be subject, unless the requirements were unnecessary in a particular situation, to the same core communicable-disease standards and procedures as are cellular and tissue-based products regulated under section 361, and would generally be subject to no additional submission requirements regarding these communicable-disease issues. To the extent that a product requiring premarketing approval were to raise additional communicable-disease concerns as a result of its source,
processing, or use, additional standards or procedures could be required in the marketing application to address these concerns.

B) Control of Processing.
1) Overview.
Row B of Table 1 differentiates products based on whether their characteristics and uses warrant handling and processing controls aimed only at preventing transmission of communicable disease (B2);
or warrant processing controls aimed at providing assurance of clinical safety and effectiveness, including but not restricted to preventing transmission of communicable disease (B3). Autologous use of cells and tissues harvested and transplanted in a single surgical procedure would be subject to no FDA oversight (B1). Regulated products used with the cells or tissues or to process the cells or tissues would continue to be regulated.

Improper handling can alter or destroy the integrity or function of cells or tissues. Improper handling also can allow cells or tissues to become contaminated (e.g, bacterial contamination during collection, processing, storage, or transplantation, or cross contamination from other contaminated tissues). Similarly, inadequately-controlled processing can alter or destroy the integrity or function of cells or tissues. Use of cells or tissues contaminated with an infectious agent obviously increases the risk of transmission of communicable disease. Use of cells or tissue with impaired integrity or function also increases the risk of transmission of communicable disease: tissue with impaired integrity or function can lead to transplantation failure, with attendant communicable disease risks (e.g., by increasing the patient's susceptibility to communicable disease, or requiring additional transplantation procedures, with their attendant communicable-disease risks.)

2) Factors Affecting Processing Concerns and Clinical Safety and Effectiveness Concerns.

As previously discussed above, the factors affecting the level of concern regarding processing controls and product safety and effectiveness are: manipulation (i.e., whether the product is minimally or more-than-minimally manipulated); homologous or non-homologous function; whether or not the cells or tissue are combined with non-cell/non-tissue components; and whether or not the product is used for metabolic function as opposed to reproductive or structural function. The agency describes these factors and their regulatory implications below.

(a) Non-cell/non-tissue components. Cellular and tissue-based products may be combinations of cells or tissues with mechanical or synthetic components, with drugs, or with non-cell/non-tissue biologics. The largest and fastest growing class of such combination products are those containing synthetic or mechanical components. These components raise concerns about function, compatibility, and durability. Examples of such combination products would include epithelial cells on a biomatrix to cover burns; allogeneic pancreas cells in a capsule that allows exit of insulin but not entry of antibodies; and bone when combined with collagen or growth factors.

The agency does not anticipate that its planned regulatory approach for cellular and tissue-based products would alter existing agency regulatory policies concerning cellular and tissue-based products containing non-cell/non-tissue components. These combination products are generally subject to premarketing requirements. The decision as to which part of the agency has primary regulatory responsibility for such combination products will depend on the primary mode of action of the product.

Combination products whose primary mode of action is that of a device are regulated by the Center for Devices and Radiological Health (CDRH). Combination products whose primary mode of action is that of a biologic are regulated by the Center for Biologics Evaluation and Research (CBER). Combination products whose primary mode of action is that of a drug are regulated by the Center for Drug Evaluation and Research (CDER). The agency intends to assure that its reviews of these products are consistently performed, regardless of which Center is responsible for the review.

For combination products with synthetic or mechanical components (which comprise the largest class of combination products), clinical trials and marketing applications must address the clinical safety and effectiveness of the overall product, as well as the function and compatibility of the synthetic or mechanical components. The agency's principal concerns with the use of these materials are that they function correctly, that they last a predictable and adequate length of time, and that they are compatible with surrounding tissue. Clinical trials would thus be required under IND or IDE, as appropriate.

The agency is setting up a Tissue Reference Group to assist in making jurisdictional decisions and applying consistent policy to these products. The agency hopes thereby to resolve expeditiously any scientific or regulatory questions that arise as to where and how such products should be reviewed. The Tissue Reference Group will consist of three CBER and three CDRH employees. It will provide a single reference point for all tissue-related questions received by the Centers or the Office of the Chief Mediator and Ombudsman.

b) Manipulation. The agency would consider processing of structural tissue to be "minimal manipulation" when the processing does not alter the original relevant characteristics of the tissue. The relevant characteristics of structural tissue are those relating to the tissue's ability to carry out the function of reconstruction and/or repair.

Thus, separation of structural tissue into components whose characteristics relating to reconstruction and/or repair are not altered would be minimal manipulation. Similarly, extraction or separation of cells from structural tissue, in which the remaining structural tissue's characteristics relating to carrying out reconstruction and/or repair were unaltered, would be considered minimal manipulation. Other examples of procedures that would be considered to constitute only minimal manipulation include cutting, grinding, and shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or gamma irradiation; cell separation; lyophilization; cryopreservation; and freezing.

In contrast, extraction of endogenous substances such as minerals or proteins from structural tissue would be considered more-than-minimal manipulation, because such modifications would ordinarily alter the tissue's relevant characteristics.

The agency would consider processing of cells (both structural and non-structural) and non-structural tissues to be "minimal manipulation" when the processing does not alter the biological characteristics of the cells or tissue. The agency would consider processing of cells and non-structural tissues to be "more-than-minimal manipulation" when the processing alters the biological characteristics (and thus potentially the function or integrity) of the cells or tissue, or when adequate information does not exist to determine whether the processing will alter the biological characteristics of the cell or tissue. Examples of more-than-minimal manipulation of cells and tissues include cell expansion, encapsulation, activation, or genetic modification.

Cells or tissues that are more-than-minimally manipulated would be subject to processing controls that generally would cover chemistry, manufacturing, and controls (CMCs), and to premarket requirements for determination of safety and effectiveness because manipulation has the potential, or is intended, to change the cell or tissue's biological characteristics or function. The agency has previously used the concept of manipulation to identify those cellular therapies for which premarket approval would be required. In the somatic cell and gene therapy statement published in October, 1993 (58 FR 53248), the agency stated:

Cells subject to licensure as final biological products when intended for use as cell therapy include cells manipulated in a way that changes the biological characteristics of the cell population.

As described for row B3 in section V B2c below, these products would continue to be subject to CMCs, including process controls and product specifications designed to ensure safety, purity, and potency, and to IND or IDE and marketing application procedures. The agency has prepared CMC guidances for some of these products.

As additional information is generated about procedures in the "more-than-minimal-manipulation" category, the agency intends to consider them to be in the "minimal-manipulation" category when

clinical data and experience show that the procedure does not alter the biological characteristics of the cells or non-structural tissue, or the relevant structure-related characteristics of structural tissue. This flexibility will permit product processing that has been found not to affect the pertinent characteristics of the product to be subjected to a lower level of regulation.

In the somatic cell and gene therapy statement, the agency stated that it considered cell selection to constitute more-than-minimal manipulation. After additional experience and deliberation, the agency now considers cell selection (e.g., selection of stem cells from amongst lymphocytes and mature cells of other lineages) to be minimal manipulation.

In cases where the agency has not made known whether it considers a particular kind of processing to be "minimal" or "more-than-minimal manipulation", individuals may request an opinion from the agency's Tissue Reference Group. Individuals who believe that a particular kind of processing is only minimal manipulation and choose to proceed without seeking clarification assume the risk that they may be out of compliance with premarketing and labeling requirements if the agency determines that the processing is more-than-minimal manipulation.

c) Homologous and non-homologous function. The distinction between homologous and non-homologous function will differ depending on whether or not the product is a structural tissue. The agency considers structural tissue to be used for a homologous function when used to replace an analogous structural tissue that has been damaged or otherwise does not function adequately. Conversely, the agency would consider structural tissue to be performing a non-homologous function when used for a purpose different from that which it fulfills in its native state, or in a location of the body where such structural function does not normally occur.

Examples of homologous uses of structural tissues include bone allograft obtained from a long bone but used in a vertebra; skin allograft obtained from the arm but used as a skin graft on the face; pericardium, a structural covering of the heart, used as a structural covering for the brain; human heart valves; and human dura mater, a fibrous covering of the brain, used as a covering. (Thus, the agency would redesignate human heart valves and human dura mater from devices to tissues subject to section 361 oversight.)

Examples of non-homologous use of structural tissue include amniotic membrane used for wound healing on the cornea, and cartilage placed under the sub-mucosal layer of the urinary bladder to change the angle of the ureter and thereby prevent backflow of urine from the bladder into the ureter. The amniotic membrane, which covers the amniotic sac in utero, would be intended to heal a damaged corneal epithelium by growing new corneal epithelial cells, a function it does not normally perform in utero. The cartilage would be acting as a structural support (its normal function), but in a location where such structural support does not normally exist.

The agency considers cellular products to be used for a homologous function when they are used to perform their native function, and for a non-homologous function when they are used to perform other functions. An example of homologous use would be hematopoietic stem cells used for hematopoietic reconstitution of individuals with marrow aplasia, chemotherapy-induced marrow ablation, Fanconi's anemia, or severe combined immunodeficiency disease. An example of non-homologous use of the same cellular product would be treatment of some adrenal leukodystrophies (which are congenital metabolic deficiencies), because the sponsor would be intending for the stem cells to perform a metabolic function other than hematopoietic reconstitution.

As for manipulation, the agency would have increased safety and effectiveness concerns for cellular and tissue-based products that are used for non-homologous function, because there is less basis on which to predict the product's behavior. Thus, a tendon used to replace a tendon, even one elsewhere in the body, is still being used for a homologous function and can reasonably be expected to function appropriately. However, without clinical trials, one cannot predict with any certainty how a tendon would act when used for a non-homologous function, such as to constrict a blood vessel to prevent pulmonary embolism.

As described above for manipulation, in cases where the agency has not made known whether it considers a particular use to be homologous or non-homologous, investigators may request an opinion from the agency's Tissue Reference Group. Individuals who believe that a use is homologous and choose to proceed without seeking clarification assume the risk that they may be out of compliance with premarketing and labeling requirements if the agency determines that the use is non-homologous.

d) Metabolic function. Products with a metabolic mode of action usually rely on viable, functioning cells (e.g., pancreatic islet cells, pituitary cells, stem cells) for function. They therefore are sensitive to perturbations and may not retain normal function after the transplantation process. Failure or improper functioning of such products often can have a broad variety of systemic adverse effects, and can be life-threatening (e.g., hematopoietic stem cell replacement after marrow ablation by chemotherapy, pancreatic islet cell therapy for diabetes). Relatively few such products have an established history of safe use. (The agency believes that some autologous and family-related-allogeneic uses of hematopoietic stem cells may have such an established history.)

As noted above, minimally manipulated cellular and tissue-based products with metabolic function raise greater clinical safety and effectiveness concerns than do products with structural or reproductive function. The agency intends to assert premarketing requirements over these products (except when the cells or tissues are used in the person from whom they were obtained or in a close blood relative of the donor, in which case as a policy matter the

agency would not require premarket submissions). Thus, for example, the agency would not call for clinical safety and effectiveness information for autologous or family-related allogeneic use of minimally manipulated hematopoietic stem cells (for which no non-homologous use promotional claims were made), but would require clinical safety and effectiveness information for non-family-related allogeneic use of the same cells. As noted in B3 above and section IV below, the agency believes that, for minimally manipulated stem cells used allogeneically to reconstitute the cellular components of blood, sufficient clinical safety and effectiveness data may exist in the near future to enable the development of processing and product standards for certain uses that would obviate the need for applicants to submit CMC and clinical safety and effectiveness information prior to marketing.

e) Reproductive function. In contrast to other metabolic tissues, reproductive tissues raise less substantial issues of rejection, graft versus host disease, or compatibility. Indeed, unlike other tissue, they perform their normal biological functions in an allogeneic setting. Failure of reproductive tissue generally does not have life-threatening or systemic adverse effects except for fertility per se. Reproductive tissues have a long history of use in the medical community. (Assessments of pregnancy success rates for live births in clinics is currently being addressed by the Centers for Disease Control and Prevention, under the Fertility Clinics Success Rate and Certification Act of 1992.)

f) Structural function. Cells and tissues used for structural purposes generally raise different clinical safety and effectiveness concerns than do metabolic cells and tissues. Many structural cellular and tissue-based products raise limited safety concerns beyond adverse local effects. Depending on location, failure of most structural cellular and tissue-based products is unlikely to lead to life-threatening consequences. In many cases, determination of effectiveness of structural therapies is more straightforward than is determination of effectiveness of metabolic therapies.

Additionally, many structural tissue-based products rely predominantly on non-living tissues (e.g., tendons) for function. They therefore usually are relatively insensitive to external factors and are more likely to retain normal function after the transplantation process. Also, many structural tissue-based products are conventional tissues having a long and established history of safe use in the medical community.

3) Regulatory requirements.
a) Row B1. Autologous cells and tissues collected and transplanted in a single surgical procedure (e.g., skin or vein grafts) would not be subjected to any regulatory requirements.

b) Row B2. Cells and tissues not collected from and transplanted into the same person in a single surgical procedure, and not having any of the factors that lead FDA to require section 351 and/or FDCA regulation (i.e., they are minimally manipulated, for homologous

use, without non-cell/non-tissue components, and not for metabolic use when from an unrelated donor), would be subject only to handling and processing requirements under section 361 of the PHS Act. The agency intends to promulgate, under section 361, good tissue practice requirements (GTPs) that would be aimed at preventing contamination and preserving product integrity and function through proper handling and processing practices. Apart from registration, listing, and reporting requirements, there would be no required FDA submissions; for example, there would be no premarketing approvals. All establishments or persons that recover, screen, test, procure, bank, process, transport or distribute cells or tissues for allogeneic use or from multiple donors would be subject to some or all of these requirements as appropriate.

Examples of B2 products would include banked tissues, such as semen, human heart valves, powdered lyophilized non-demineralized bone and other conventional tissues, as well as banked autologous and banked or unbanked family-related allogeneic peripheral and placental/umbilical cord blood stem cells.

c) Row B3. Inadequately controlled or otherwise improper processing can result in products that are ineffective, and in products that are unsafe for reasons other than increasing the risk of transmission of communicable disease. For example, products may be unsafe because they are ineffective (e.g., nonviable stem cells used for hematopoietic reconstitution after chemotherapy) or because they function improperly (e.g., cells or tissue that inappropriately secrete a hormone may cause unwanted metabolic effects). Thus, processing controls for products that raise such clinical concerns often must be more comprehensive than those needed to address risks of transmission of communicable disease.

As discussed in sections IV and V, cellular and tissue-based products that are more-than-minimally manipulated, or are used for non-homologous function, or in combination with non-tissue components, or for a metabolic purpose raise a higher level of processing concerns pertinent to assurance of clinical safety and effectiveness. The agency would subject such products/uses to processing-controls under section 351 of the PHS Act and/or under relevant sections of the FDCA.

Such processing controls generally would cover product chemistry, manufacturing, and controls (CMCs) and be subject to premarket submissions. However, if FDA determines that class-wide standards can be developed such that products in a specified product class are known to be clinically safe and effective when manufactured in accordance with certain defined product specifications and process controls, FDA could establish such standards through rulemaking and require premarketing submission of certification by the applicant that the products met the published standards, rather than a more detailed submission of the clinical data.

For non-family-related allogeneic cord or peripheral blood stem cells for hematopoietic reconstitution, which in some cases have been studied without an investigational new drug exemption (IND), the agency intends to call for a phase in of IND and licensure

submissions (see section VI, Implementation of Regulatory Procedures). If, prior to the end of the phase-in period, the agency has received adequate data and information to enable the agency to promulgate standards designed to ensure safety and effectiveness for particular uses of these products, FDA anticipates making a class-specific finding of safety and effectiveness for products meeting those standards (see section V C, Clinical Safety and Effectiveness, and section VI, Implementation of Regulatory Procedures) . Individuals pursuing licensure subsequent to the adoption of such standards would not have to submit clinical safety and effectiveness data to the agency in their premarketing applications, but would merely have to certify that they meet the standards.

Examples of B3 products used for metabolic function would include hematopoietic stem cells intended for use in recipients who are not close blood relatives of the cell donor or for uses other than to reconstitute the cellular components of the blood; cloned and/or activated lymphocyte therapies for cancer or infectious diseases; and hematopoietic stem cells that have been expanded or modified as part of gene therapy.

Examples of B3 products used for structural function would include demineralized bone (which the agency plans to propose to classify as a class I device and to exempt from premarket submissions), and bone combined with collagen or growth factors.

C) Clinical Safety and Effectiveness - Use-specific Concerns.
1) Overview.
Row C of Table 1 distinguishes products based on whether they have none of the factors relating to clinical safety or effectiveness that would lead FDA to require section 351 or FDCA premarketing submissions requirements (C1); whether they have one or more of such factors and are used to achieve a local structural function (i.e., reconstruction or repair) (C2); and whether they have one or more of such factors and are used to achieve a reproductive or metabolic function (C3).

Products described under C1 would be subject to no section 351 or FDCA requirements for clinical trials demonstrating safety and effectiveness. Products under C2 and C3 would be subject to section 351 and/or FDCA requirements. Requirements for premarket clinical data submissions for C2 and C3 cellular and tissue-based products would generally be as for other regulated products, tailored as appropriate to the characteristics of the product and the concerns raised by the specific indication and product. For serious and life-threatening illnesses, all other applicable policies (e.g., expedited review, treatment IND, accelerated approval) would be available to help speed product availability.

C2 products are separated from C3 products to indicate that in general they would be subject to different safety and effectiveness endpoints to fulfill clinical trial requirements. Clinical trial requirements for C2 products (whether regulated as biologics or devices) would generally be consistent with those for devices for the same indication, whether regulated under INDs or IDEs (investigational

device exemptions). Clinical trial requirements for C3 products would generally be consistent with those for new drugs or biologics for the same indication.

2) Regulatory Requirements.
a) Row C1. FDA would not require premarket review and approval for cellular and tissue-based products that are minimally manipulated, are used for homologous function, do not contain non-cell/non-tissue components, and are for structural or reproductive use. Such products raise relatively limited clinical safety and effectiveness concerns, and thus would not be subject to premarket submission of clinical data. Additionally, as a policy matter the agency would not require premarket submission of clinical data for cellular or tissue-based products that are minimally manipulated, are used for homologous function, do not contain non-cell/non-tissue components, and are for metabolic use, when they are to be used autologously or in a close blood relative of the donor. Communicable-disease risks would be addressed under section 361 as discussed above in sections VI, A, 2, and VI, B, 2.

Examples of such products would include heart valve and dura mater transplants, vein grafts, tendons to repair or replace tendons, autologous or family use of peripheral or cord blood stem cells for hematopoietic reconstitution, and human gametes (sperm and eggs), zygotes, and embryos intended for insemination, fertilization, or transfer.

b) Row C2. The agency recognizes that cellular and tissue-based products for structural use raise different safety and effectiveness issues than do products for metabolic or reproductive use, and that they can be evaluated in a manner generally consistent with that of devices for the same indication, modified as appropriate for the nature of the product. (They may also be classified as devices). The agency outlined its approach for evaluating a major subset of such products in the May, 1996 Guidance on Applications for Products Composed of Living Autologous Cells Manipulated Ex Vivo and Intended for Structural Repair or Reconstruction (MAS Cells) and the CMC Guidance for Autologous Cell Therapy (1997).

The agency recognizes that many of the highly manipulated cellular and tissue-based products intended for structural purposes often will be used for the same indication as are some devices, or will be classified as devices. It is the intent of CBER and CDRH to ensure consistent review of such products, whether regulated as devices or biologics, and to establish clinical effectiveness standards for structural cells regulated as biologics that would be consistent with those existing for comparable devices. However, different products may raise different safety, effectiveness, or durability concerns, and may be amenable to different methods for measuring outcomes.

Some examples of C2 cellular and tissue-based products include manipulated cells for autologous structural use (MAS cells) such as expanded chondrocytes to repair damaged knee cartilage, and devices such as demineralized bone. (The agency does not intend for

demineralized bone used alone to be subject to premarket submission requirements. The agency plans to propose to classify demineralized bone as a class I device and to exempt it from premarket submissions, as described in section VI.)

c) Row C3. Some examples of C3 cellular products include autologous genetically-manipulated cellular therapies involving correction of genetic defects, non-family-related allogeneic cord or peripheral blood stem cells, stem cell therapies involving growth factors such as interleukin-3 and stem cell factor or gene therapy, activated lymphocytes for treatment of cancer, and cloned lymphocytes for the treatment of HIV infection or other infection. (See section VI A below regarding phase-in of licensure requirements for non-family-related allogeneic cord and blood stem cells.)

D) Promotion and Labeling. Row D of table 1 addresses the issue of potentially false or misleading claims. For cellular and tissue-based products regulated under section 361, labeling would need to be clear, accurate, balanced, and non-misleading. Such labeling could include what the tissue is and how it has been processed; the homologous uses of the tissue; and the communicable-disease screening, testing and quarantine procedures that were followed and results obtained. FDA intends to propose regulations to address labeling requirements under section 361 of the PHS Act.

Products that are intended or promoted for use for a non-homologous function would fall outside the scope of the section 361 regulation the agency intends to promulgate, and would be subject to regulation as biological drugs or devices under section 351 of the PHS Act and/or the FDCA. For cellular and tissue-based products regulated under FDCA and/or section 351 of the PHS Act, the agency intends to regulate labeling under existing authorities therein.

E) Monitoring and Education. At present, FDA does not know the full size and scope of the cell and tissue industry and its potential products. The agency believes that, in order for it to understand the issues raised by these new products and be able to educate the industry and keep it up to date regarding FDA policies, guidances, and requirements, as well as to enable the agency to inspect establishments for compliance with applicable laws and regulations, all establishments that recover, screen, test, procure, bank, process, transport or distribute cells or tissues from multiple or allogeneic donors, should register and list their products with FDA. Therefore, the agency would require registration and listing for all such establishments and products over which FDA is asserting its jurisdiction under section 361 of the PHS Act, section 351 of the PHS Act, or the FDCA. The agency is developing a simple electronic filing system that it will use for establishment registration and product listing. Registration and listing for products subject to section 361 oversight would not be required until the electronic system is in place.

FDA does not intend to require that it be sent reports of errors and accidents that occur during processing and distribution of cellular

and tissue-based products subject to section 361 controls. However, as part of the GTP requirements, establishments and persons will be required to identify and investigate errors and accidents, take appropriate corrective action, and maintain records of such failure assessments. The agency does intend to propose post-market adverse event reporting requirements relating to transmission of communicable disease.

The agency intends to apply registration and listing requirements in section 510 of the FDCA as well as existing post-market reporting requirements to those cellular and tissue-based products subject to regulation under section 351 of the PHS Act and/or the FDCA. The agency intends to propose regulations for registration, listing, GTPs, and post-market adverse event reporting of those cellular and tissue-based products regulated under section 361 of the PHS Act.

VI. IMPLEMENTATION OF REGULATORY PROCEDURES

The agency intends to implement this regulatory plan in a step-by-step fashion. The agency intends to promulgate through notice and comment rule-making new regulatory requirements, and to allow for phase-in as appropriate. Some examples of how FDA intends to implement this regulatory plan for selected products are as follows.

A) Stem cells. The agency intends to phase in its regulatory oversight of minimally manipulated hematopoietic stem cells derived from cord or peripheral blood and used for hematopoietic reconstitution in patients who are not close blood relatives of the donors from whom the cells were obtained. (Minimally manipulated hematopoietic stem cells to be used for their normal function in the person from whom they were obtained or in a close blood relative would be regulated under section 361, and would not be subject to premarket application requirements.) The agency intends to phase in regulation of allogeneic use of these products as follows.

1) Registration and Listing. FDA intends that all facilities that recover, screen, test, procure, bank, process, transport or distribute stem cells, derived from umbilical cord blood or peripheral blood, to treat, cure, diagnosis, or mitigate diseases in humans, be required to register with the FDA and list the products at their facility. Registration and listing would be accomplished through an electronic system that the agency is developing.

2) Communicable-Disease Screening and Testing. The agency intends to require testing of blood samples from allogeneic donors of hematopoietic stem cells in order to prevent the transmission of communicable diseases. For peripheral blood stem cell donors, the donor's blood, and for umbilical cord blood donors, the mother's blood, would be required to be tested for HIV, cytomegalovirus, HTLV, syphilis and hepatitis infection (i.e., HBsAg, anti-HIV-1, anti-HIV-2, HIV-1-Ag, anti-HTLV-I/II, anti-HCV, a serologic test for syphilis, and anti-CMV). The medical history and physical examination of prospective donors would include screening for high risk for HIV and hepatitis, Creutzfeldt Jacob Disease (CJD), and tuberculosis.

The agency intends to recommend, but not require, that testing be performed when the stem cells will be used in the person from whom they were obtained. In such case, the agency would recommend only the following tests: HBsAg, anti-HCV, anti-HIV-1, anti-HIV-2, HIV-1-Ag, and anti-HTLV-I/II. The agency also would recommend that the history and physical examination of the donor include screening for high risk for HIV and hepatitis. The agency would require that record-keeping and labeling reveal which of the recommended tests were performed, and the results obtained from those tests, as well as which of the recommended tests were not performed. Appropriate labeling would be as follows: "tested and negative", "tested and positive", or "not tested for biohazards".

Ordinarily, cells or tissue would not be collected from a donor testing positive for any of these viruses, and if collected would be required to be destroyed. However, the agency recognizes that there may be circumstances justifying storing or using such cells or tissues. For example, in cases where a stem cell donor tests positive for a virus or has been found to be at risk of infection (even if testing negative), and the stem cells are intended for autologous use, for use in a close blood relative, or for use in a transplant recipient with a rare histocompatibility match, the agency intends to require that 1) the cells be labeled "BIOHAZARD", 2) autologous products also be labeled "FOR AUTOLOGOUS USE ONLY", 3) written advanced informed consent of the recipient be documented, and 4) there be documented concurrence of the recipient's physician before the cells could be released from a cell bank.

3) Processing Standards. The agency intends to promulgate establishment controls, processing controls, and product standards under section 351 of the PHS Act. For minimally manipulated stem cells used for hematopoietic reconstitution, the agency believes that it may be possible to develop product standards (including manufacturing controls and product specifications aimed at ensuring product safety and efficacy) from existent published clinical trial data or data developed in the near future. FDA intends to invite professional groups and individuals to submit to the agency data and standards that they believe would ensure safety and effectiveness. If sufficient data are not available to develop processing and product standards after a specified period of time, the stem cell products would be subject to IND and marketing application requirements.

FDA intends to list in the Federal Register relevant questions for developing the data and standards, and the deadline for submission of responses. Examples of the kind of information that the agency believes will be necessary to have in standards include criteria for acceptance of a unit (such as volume, storage temperature limits, limits on microbial or other contamination, viable cell number, and functionality), and procedures for handling, transporting, storing, and thawing materials, and for when and how contamination and viability testing should be carried out.

Upon development and promulgation of standards designed to ensure safety, purity, and potency, FDA would issue licenses based on a

certification by the applicant that the standards are met. The certification could be made in the same submission as the registration and listing. FDA would issue a license based on the certification submission.

During the interim period, FDA would not call for licensure of such products for unrelated allogeneic use, but would require establishment registration and product listing. The agency also could perform inspections for applicable GMP compliance, and could take enforcement action against facilities as needed (for example, because of lack of appropriate communicable disease-testing).

B) Demineralized bone. FDA would consider demineralized bone (decalcified freeze dried bone allograft) to be an unclassified pre-Amendments device rather than a tissue under section 361 because the bone is more-than minimally manipulated. FDA would seek a classification recommendation from the Orthopedic/Dental Advisory Panels. The device to be classified would be defined as including allograft bone that is processed ONLY to demineralize and preserve the bone, and ONLY intended to be used as a bone filler in orthopedic and/or dental procedures.

Based on current information, FDA expects to propose that demineralized allograft bone be regulated as a Class I medical device exempted from premarket notification. In addition, FDA expects that it would also propose to exempt demineralized allograft bone from the GMP requirements except for certain requirements consistent with those proposed for human tissues regulated under section 361.

To ensure that the GMP requirements applicable to demineralized bone are ultimately consistent with the requirements for human cellular and tissue-based products regulated under section 361, the Federal Register documents regarding the requirements for each would be published as companion documents.

VII. CONCLUSION

The agency believes that the above-described proposed approach to the comprehensive regulation of cellular and tissue-based products would provide adequate protection of public health, both from the risks of transmission of communicable disease and from the risks of therapies that may be dangerous, while enabling investigators to develop new therapies and products with as little regulatory burden as possible. The agency intends for this regulatory scheme to encourage research and innovation, while at the same time set boundaries between the kinds of experimentation with human products that warrant only minimal FDA oversight and the kinds of experimentation with human products that warrant greater FDA oversight.

GLOSSARY OF TERMS AS USED IN THIS DOCUMENT

ablation	Removal or destruction

allogeneic use — Cells or tissue transplanted from one person to another.

autologous use — Cells or tissue removed from and transplanted back into the same person.

close blood relative — A first degree blood relative (i.e., parent, child, or sibling).

cord blood — Blood in the placenta and umbilical cord, e.g., blood taken at the time of birth

family relative — A first degree blood relative (i.e., parent, child, or sibling).

hematopoietic — Giving rise to the cellular elements of the blood (e.g., white blood cells, red blood cells, platelets).

hematopoietic stem cells — Cells capable of generating white blood cells, red blood cells, and platelets. For the purposes of this document, these would include progenitor cells that are committed to develop into a particular cellular lineage. Hematopoietic stem cells presently can be collected (as a very small fraction of the cells) from peripheral blood, placental/umbilical cord blood, and bone marrow, often for transplantation into patients whose own hematopoietic stem cells have been destroyed by anticancer treatment or disease.

homologous function — Use for the normal function of the cell or tissue, and, for structural tissue, use for a structural purpose in a location of the body where such functional purpose normally occurs (see P. 15).

MAS cells — Manipulated Autologous cells for Structural use.

metabolic use — For systemic effect.

minimal manipulation — Processing that does not alter the biological or relevant functional characteristics of cells or tissue (see P. 13).

more-than-minimal manipulation — Processing that alters the biological or relevant functional characteristics of cells or tissue (see P.13).

non-homologous function — Use for other than the normal function of the cell or tissue, or for structural tissue, use for a structural purpose in a location of the body where such functional purpose does not normally occur (see P. 15).

peripheral blood — Circulating blood (in contrast to, for example, blood in bone marrow).

reproductive tissue — Semen, ova, embryos.

reproductive use — To treat infertility.

stem cells — Cells capable of replicating themselves and of generating more-differentiated daughter cells.

structural use — For anatomic reconstruction or repair.

unrelated — Someone other than a close blood relative.

Table 1 Relationaships among product concerns, product characteristics, regulatory approaches

Table 2 Regulatory Framework for Cells and Tissue Related Products

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NOTE: This ASCII version does not contain Tables 1 and 2. A printed copy is available by mail or FAX by calling 1-800-835-4709.

**********========== ATTACHMENT 1 ==========

ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:

RFC-822-headers:

Received: from gatekeeper.eop.gov by PMDF.EOP.GOV (PMDF V5.0-4 #6879) id <01IG2IES4LQO00I0KE@PMDF.EOP.GOV> for Jennifer_J._Kulynych@oa.eop.gov; Mon, 03 Mar 1997 14:43:05 -0500 (EST)

Received: from cber.cber.fda.gov by gatekeeper.eop.gov; (5.65v3.2/1.1.8.2/17Oct95-0424PM) id AA02396; Mon, 03 Mar 1997 14:42:25 -0500

Received: from mr.cber.fda.gov by CBER.CBER.FDA.GOV (PMDF V5.0-8 #17218) id <01IG2HUB8XOG8X151Z@CBER.CBER.FDA.GOV> for Jennifer_J._Kulynych@oa.eop.gov; Mon, 03 Mar 1997 14:27:35 -0500 (EST)

Received: with PMDF-MR; Mon, 03 Mar 1997 14:17:54 -0500 (EST)

X400-MTS-identifier: [;45714130307991/215320@FDACB]

========== END ATTACHMENT 1 ==========

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: acapron@Law.usc.edu (acapron@Law.usc.edu [UNKNOWN])

CREATION DATE/TIME:19-MAR-1997 14:27:26.00

SUBJECT: Re: More thoughts on cloning:

TO: nbac-members@lists.Princeton.EDU (nbac-members@lists.Princeton.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
On Wed, 19 Mar 1997 bernie@itsa.ucsf.edu wrote:

>
> 1. I re-read the 1982 report Splicing Life, by the President's
> Commission and found it most interesting. Evidently the impetus for this
> report was a letter from three religious leaders to President Carter
> expressing concern over genetic engineering. I would be most interested
in > any comments by those who participated in that earlier Commission.
Would > it be useful for us to invite organized religious groups to
present their > views? Having professors give their opinions on what
religions would say > isn't quite the same as asking the religious leaders
directly. Following > on my concerns about leaving voices unheard, should
we invite leaders of
> fundamentalist, born-again groups to present their views, which may be
> different from the Protestant views we heard last week. My own belief
is > that it is better to hear before we write our report how vocal
minorities
> will respond. Even if we think we know what they will say, it may be
> helpful (and politically sage) to listen to them directly.

Two comments:

A. Since the Commission's work was in some sense a response to the concerns voiced by the three major umbrella organizations for Catholics, Protestants, and Jews, it made sense to have formal statements from them, esp. because we expected (as turned out to be the case) that such statements would be much less alarmist than the views written by Jeremy Rifkin that the groups' leaders were initially persuaded to send to President Carter. As I recall, in fact, several of the organizations basically said, in effect, "we don't have much doctrinally to contribute on this subject."

B. In the present circumstance, I agree it is useful to know where the potential players stand before issuing a report than afterwards. Obviously, in inviting the religious groups to share their views with us, we aren't "commissioning" papers from them nor promising them time on our agenda (expect during public comment); we have to husband our resources (including time) and I suspect that much of what we hear (if very many groups actually follow through and submit statements) will be quite similar (perhaps sorting in two or three different groups). As is going to be true for a lot of the material we get (both that which we

commission and that which comes in "voluntarily"), we will need a staff member to sort through any such statements and prepare summaries and syntheses of them (some textual, and perhaps preliminarily in a chart in which the contributors and their positions/conclusions are organized).

> 2. The Splicing Life report organized ethical concerns into two
> main categories: Concerns about playing God and Concerns about consequencs.
> Would a consequentialist/nonconsequentialist distinction be helpful in
> organizing our report?

Yes, I think the objections on grounds of inherent rightness/wrongness and on consequentialist grounds would probably be useful here as well. We can probably borrow from SPLICING LIFE some of the material on the "playing God" argument (esp. from the religious views that for "people of the Book," man [& woman] are SUPPOSED to be co-creators, in the sense of changing the world ... provided that we must do so responsibly; all of medicine is in this sense "playing God").

> 3. Would it be helpful to analyze specific scenarios which are
> offered as situations in which cloning a human being would be justified?
> The ones commonly discussed are the infertile couple who has a dying child, > an infertile couple who are Holocaust survivors, or a couple with a child
> with leukemia who needs a bone marrow transplant. I am stuck that many
> such cases involve cloning a child, who may not be capable of giving
> informed consent. Furthermore, I'm not clear what the benefits would be of
> cloning a child with leukemia in order to get stem cells for
> transplantation.
>

Yes, I think it would be useful to discuss such scenarios. My personal inclination would be to discuss them EARLY as a way of teasing out the reasons for and against, and then go on to examine those reasons.

As for the specific objection: I share the sense that the stem cell example is problematic (here, we can look at the same concern that has been raised about banking stem cells from cord blood: in the case of neoplastic disease, a question has been raised whether one would even want to use autologous cells as treatment and whether it wouldn't be better to use "well matched" cells from another donor).

One other example is comparable to what is being talked about with the racehorse Cigar (and interesting that racing assn forbids even AID and apparently also IVF and by implication cloning....stronger rules for horse than for humans, though for different reasons!). The situation is one of the potential parent (male or female) who does not produce gametes. The argument (comparable to the Holocaust survivor one) is that the person has a strong interest in having a genetically related offspring and that there is no other way for this to occur. The contra-arguments have to do with whether this makes too much of genetics (and that implications of that view for a lot of other subjects) as well as

the consequentialist and nonconsequentialist arguments about "using" a child-clone in this fashion.

Alex

****
* Alexander M. Capron acapron@law.usc.edu *
* Henry W. Bruce Professor of Law (213) 740-2557 (voice) *
* University Professor of Law and Medicine (213) 740-5502 (fax) *
* University of Southern California (213) 740-0149 (fax) *
* Los Angeles, CA 90089-0071 *
****

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Rachel E. Levinson (CN=Rachel E. Levinson/OU=OSTP/O=EOP [OSTP])

CREATION DATE/TIME:20-MAY-1997 14:30:37.00

SUBJECT: Re: Ethics, part II

TO: nbac-members (nbac-members @ lists.Princeton.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
See edits in brackets in very last paragraph

bernie @ itsa.ucsf.edu
05/15/97 02:29:39 PM
Please respond to nbac-members@lists.Princeton.EDU
Record Type: Record

To: nbac-members @ lists.Princeton.EDU
cc:
Subject: Ethics, part II

VIII. Cloning research involving human embryos.
Any research on cloning human beings through nuclear transfer from somatic cells would involve human embryo research. The fusion of a human somatic cell and a oocyte whose nucleus has been removed would produce a human embryo, with the potential to be implanted in utero and develop to delivery. Currently, federal funding for human embryo research is severely restricted. Congress has inserted restrictions on embryo research into the 1996 and 1997 Appropriations Bills. Congress forbids human embryo research that leads to the destruction or discarding of human embryos. Furthermore, research may not present more than minimal risk to the embryo. In addition, a 1994 Executive Order [delete Executive Order and insert "Presidential directive"] forbids federal funding for the creation of human embryos expressly for the purpose of research. Kathi, Rachel, is this an accurate description of current federal policy?
Although federal support for human embryo research is heavily restricted, there are few restrictions of human embryo research carried out in the private sector, using nonfederal funds.
From a scientific viewpoint, progress in understanding molecular genetics and cellular differentiation currently can proceed through research using [human and] animal cells and animals. Far more animal research would be required before promising therapeutic ideas, such as embryonic stem cell transplantation for leukemia, liver failure, or diabetes, could be

considered in humans. Thus cloning raises no pressing scientific reason to reconsider current restrictions on federal funding for human embryo research.

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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: holtzman@mpi.com (holtzman@mpi.com [UNKNOWN])

CREATION DATE/TIME:22-MAY-1997 07:27:55.00

SUBJECT: Ethics: Cellular Therapies

TO: nbac-members@lists.Princeton.EDU (nbac-members@lists.Princeton.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
Bernie:
late in the ethics chapter you ask for examples of cellular therapies (in addition to recombinant proteins).

all of this work is in early stages, in clinical trials. the efforts can be grouped into 3 buckets.

1- Cells to Produce a Needed Protein: deliver the cells that produce the needes hormone, enzyme, etc. as an alternative to delivering the protein itself either for better health of the patient, ease of administration or because the protein can't be effectively delivered (e.g., blood-brain barrier problems. Examples are encapsulated human fetal or porcine pancreatic insulin-producing beta islet cells, and human fetal (for treatment of diabetes)or porcine or human fetal dopamine-producing neuronal cells (for treatment of Parkinson's disease.
--Here, one would would like a continous human cell line, based on a stem cell population, of such cells that was immunologically naive so that you wouldn't need to encapsulate, would have a universal-donor cell line, would not have to worry about immunological rejection, etc.. In virtue of being a single source cell line (as opposed to individually based therapies with a new population of cells each time)you would have enhanced safety because of enhanced quality control. Research is going on the derive such cell lines from the early embryo.

2- Cells to Replace Damaged/ Depleted Cells: the object here to provide the lost multiple functions of the damaged or depleted cells. Most advanced example is the reconstitution of the various hematapoeitic lineages, e.g., after chemotherapy. Expansion of these lineages in vitro (from autologously derived hematapoietic stem cells) with transplantation back to the autologous donor is already occuring in humans. Research, earlier stage, is taking place with stem cells for additional cell lineages, e.g.,
nerve cells (for nerve damage) and mesenchymal stem cells (for carilage/bone damage).
--Again here, while the current work in clinicals with human cells starts with somatically derived, autologous lineage specific (stem cell) population, The ideal would be universal cells "in a bottle", as opposed to an individualized procedure each time. The cutting edge research looks to the embryo as the potential source of such universal donor cells.

3- Discovery of Novel Growth Factors: the developing embryo generates an

enormous number of signaling molecules/growth factors that orchestrate the differentiation of the totipotent, and then pluripotent cells of the embryo into the defined cell lineages that become the different parts of the body.
Isolation of these factors, and understanding their roles and interplay, could lead to new therapies in which we could direct cells to differentiate into needed lineages (repair damage/replace deleted lineages) or redirect cells (e.g., block/antagonize the factors to stop proliferation in a cancer or, more starwars, dedifferentiate a differentiated cell poplulation and redirect the newly created "stem cell population" to another lineage).

Hope this helps,
-steve

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: greider@cshl.org (greider@cshl.org [UNKNOWN])

CREATION DATE/TIME:23-MAY-1997 14:26:48.00

SUBJECT: Re: Ethics chapter

TO: nbac-members@lists.Princeton.EDU (nbac-members@lists.Princeton.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
Dear Bernie,

Thank you for the (FAST) revised version of the ethics chapter. I feel it is much improved. I have made some suggestions to the text and I am attaching the word 5.1 file with the suggestions. (I can later send other file types but for the moment I do not have translators since my computer crashed).

I do not understand Zeke's reservation with the new version of this chapter. I don't think that the manner in which the issue of genetic determinism is addressed weakens any argument. Rather it brings the arguments into line with reality. Perhaps if Zeke were more specific about what language he has a concern with I could find a way to address the issue.

Below are a few of the more substantive comments that I have made.

1) you write:

This report does not discuss cloning of DNA sequences and somatic cell lines and cloning research involving human embryos. Ethical questions surrounding these issues have already received extensive analysis and deliberation.

I don't know that ethical questions about cloning research involving human embryos has been extensively deliberated.

I suggest this instead:

"This report does not discuss cloning of DNA sequences and somatic cell lines. Ethical questions surrounding these issues have already received extensive analysis and deliberation. In addition we do not discuss and research involving human embryos as this area was the subject of a full report by the embryo research panel."

2) I still feel that the section entitled: "Claims that cloning would benefit society by reproducing an exemplary individual" should be eliminated. (I still feel that the section is not necessary, we state in the introduction that by reproducing an exemplary individual is science fiction, not reality. I do not see the use in discussing this issue in detail in an entire section.

I do understand the argument that some people THINK they can reproduce an exemplary individual, and even this intention might be harmful. But that is not how this section is written. The issue of a child being harmed by the parent THINKING they can choose the person the child will be is already discussed in a separate section.

3)You write:

In summary, Commissioners reached several conclusions on ethical considerations to guide public policy regarding generating children through nuclear transfer from somatic cells:

I can agree to most of the things that you say we all agree. I am not sure however why is starts with several things that "all commissioners" agree to and then goes to "some" commissioners agree and then back to all commissioners. Perhaps this section could be restructured a bit.

4) Did you intend the section on cloning DNA sequence and cell lines and Embryo research to be addendum separate from the ethics section? Althought you said it was cut it was still after a page break in the document. I still feel that we should not include this even as an addendum to the ethics chapter. We have already mentioned these issues in the introduction and said that we are not addressing them.

- ethics5=22.CWG.doc========== ATTACHMENT 1 ==========
ATT CREATION TIME/DATE: 0 00:00:00.00

TEXT:
7#wvvvvv

@Y@[_xceimos
Need quote from RTL group

"Science is close to crossing some hor
rendous boundaries" Leon Kass in Time Magazine March 10, 1997

"If objectors to
cloning can identify no greater harm than a supposed affront to the dignity of the human species, that is a flimsy basis on which to erect barriers to scient
ific research and its applications." Ruth Macklin, testimony.

"Enough good
uses can be imagined that it would be unwise to ban all cloning and cloning re
search because of vague and speculative fears." John Robertson, testimony.

"It's a horrendous crime to make a Xerox of someone" Jeremy Rifkin, Time Magazi
ne March 10, 1997

"A person who would want to clone himself is overwhelmingly
self centered"
Richard McCormick Newsweek Magazine March 10, 1997

"If research into human cloning does move forward we must ensure that it does not seek knowledge for its own sake or only to promote monetary gain or individual fame, but to serve and protect the common good. Nancy Duff testimony.

As these quotes illustrate, the birth of Dolly through nuclear transfer cloning technology, evoked widespread public discussion. Many people expressed concerns and fears about the generation of children using this technology, while others suggested that cloning may be acceptable under some circumstances. In its deliberations, NBAC attempted to understand these diverse reactions.

Many people resort to self-evident philosophical principles, scriptural passages, or religious doctrine to justify their views on cloning. Often it is hard to articulate the precise nature of ethical concerns or objections about nuclear transfer cloning. Yet in order to form public policy, we must try to express our moral concerns as clearly and explicitly as possible, so that others can understand them and consider whether they are persuasive. We must realize that in a pluralistic society, other people may not share our starting points. Furthermore, we must appreciate that even though our religious beliefs may be crucial in shaping our personal views, because the First Amendment requires separation of church and state and does not permit public policy to be based solely on explicitly religious beliefs.

This chapter has three goals. The first is to articulate and analyze the moral arguments that have been offered regarding generation of children through nuclear transfer of somatic cells. Our second goal is to offer a framework for further deliberation of the moral issues pertinent to public policies regarding such cloning. The third goal is to clarify which ethical considerations should guide public policy about nuclear transfer cloning at this time.

We have structured this chapter in the following way. In the first two sections of the chapter, we analyze the moral considerations that may be pertinent when an individual person judges whether a particular act of nuclear transfer cloning is justified. We start by considering hypothetical cases in which a baby is produced through nuclear transfer cloning. In daily life, people are accustomed to deliberating on whether an individual act is right or wrong. Examining specific cases helps us to understand the moral dimensions of an issue and to articulate the reasons for our judgments. In addition, careful reflection on particular cases can suggest what general restrictions and limits might be appropriate if public policy does not create an outright prohibition.

The various types of moral considerations are organized into two broad groups. Some arguments examine the consequences of generating a child through nuclear transfer cloning, which are alleged to be harmful or beneficial. Consequences may affect either individuals or important shared social values. Other arguments do not refer to the consequences of nuclear transfer cloning, but instead allege that nuclear transfer cloning is wrong in itself or that people have a right to use this new technology.

The third section of this chapter presents a framework for moral deliberation about public policies regarding nuclear transfer cloning. The Commission was asked to consider whether public policy should permit, regulate, or prohibit generation of children through nuclear transfer from a somatic cell. We note that our views on whether cloning is acceptable as public policy may differ from our views of whether specific acts of cloning are morally acceptable.

There are some actions that we consider morally wrong, but would not want to prohibit through public policy. Even though we might try to persuade a relative or friend that certain actions are wrong, we may not want the government to prohibit people from acting according to their own moral judgments. For example, some people may disapprove of gambling or divorce, yet oppose a governmental prohibition of these activities.

In the fourth section, the Commission indicates which arguments it believes should guide policy recommendations on generation of children through nuclear transfer of somatic cells at this time.

This report does not discuss cloning of DNA sequences and somatic cell lines and cloning research involving human embryos. Ethical questions surrounding these issues have already received extensive analysis and deliberation. In addition we do not discuss and research involving human embryos as this a area was the subject of a full report by the embryo research panal.

Ethical arguments offered to oppose acts of generating children through somatic cells nuclear transfer.

This section examines the arguments offered against generation of children through somatic cells nuclear transfer, starting with arguments claiming that such cloning causes unacceptable harms or risks. Some of these alleged harms fall on individuals, while others affect social values. Subsequently, we examine arguments claiming that cloning is wrong in itself, independent of any consequences it causes.

Arguments that cloning of children through nuclear transfer of somatic cells is unethical because of harmful consequences.

Alleged harms to individuals

The risks to the child born after cloning are unacceptable at present

The risks of attempting to clone a child through nuclear transfer from somatic cells are prohibitive at the present time, compared to the likely benefits. The technique that produced Dolly was successful in only one of 277 attempts. The success rate of cloning human beings using the nuclear transfer technique might also be extremely low (cite Science chapter). Nuclear transfer cloning involves significantly greater manipulation of genetic material than current forms of assisted reproductive technologies, and such manipulations increase the risk of birth defects. In addition, nuclear transplantation may transmit DNA that has acquired genetic mutations or has been damaged by aging. The risk of cancer or premature aging may be increased in the child that is born. The burden of proof to justify an experimental technique that may cause physical harms to children who will be born falls on those who would carry out the experiment. Before considering even the possibility of producing a child through nuclear transfer, we would require animal studies demonstrating a much higher success rate that at present and long-term safety. We would never consider using a medical drug or device on a human being after only one animal experiment. Without such extensive animal research, no conscientious physician or Institutional Review Board could approve of attempts to use nuclear transfer to generate a human child. Even if a person or couple requested cloning as a clinical intervention, it would be unethical for a physician to provide it, in light of current limited knowledge about the feasibility and safety of the procedure. For these reaso

ns, the Commission unanimously supports prohibitions on all attempts to produce children through nuclear transfer from a somatic cell at this time.

Critics are concerned about psychological as well as physical harms to children born after cloning. Such concerns are discussed in the following sections.

Claims that children born after cloning through nuclear transfer from somatic cells would be subjected to inappropriate attempts at control

Some people have suggested that cloning offers more control over the genetic makeup of the child than existing methods of genetic selection, such as selecting a partner or using genetic screening to avoid serious illness, because the genes of the child would be the same as those of the nuclear donor rather than being a random combination of genes from two parents. In addition, cloning allows positive selection of desirable genes, rather than negative avoidance of undesired genes. [This is always true, not unique to cloning, selction of a partnerallows selection of desirable traits]

Novels and plays about cloning dramatize fears about such an ability to duplicate the genes of an individual. Evil dictators are portrayed as making multiple copies of a given individual to serve as warriors or drones to work in factories. Of course, even without making genetically identical individuals it may already be possible to train a cadre of soldiers or workers through existing techniques of social control. However, these stories reveal misunderstandings that some people have about the role of genes in determining the individual. As described in the introduction and the science chapter, a child that resulted from nuclear transfer cloning would have only the genes, not the characteristics and behaviors of the nuclear donor.

Efforts to use nuclear transfer from a somatic cell to control the childs character are futile because they are based on a view of genetic determinism that is scientifically invalid. Nonetheless, critics fear that after birth the child would be subjected to the will of the parent in inappropriate ways. Parents use their own nuclei to creat a child who clone their genetic makeup may view these children as a younger versions of themselves, whose interests and activities they control more strictly than with other children. Excessive attempts at control may harm the child, even though the efforts are fruitless.

In rebuttal, others believe that parental attempts to control children resulting from nuclear transfer cloning will not be essentially different from what parents already do and indeed are expected to do when rearing children. Parents already try to mold their children through selecting a partner, providing education, and bringing up the child in a chosen religious faith. Children usually learn to handle excessive parental attempts to control them and are able to develop as individual persons.

Claims that children born after cloning through nuclear transfer from somatic cells would have inappropriately restricted future life scenarios

The generation of children through nuclear transfer of somatic cells deliberately attempts to replicate the genetic composition of an existing person. Some critics fear that parental expectations will then be very specific. The child may always be compared to the person who donated the nucleus, even if parents acknowledge that education and environment will play a crucial role in who the child will become. Children born using nuclear transfer may be judged in terms of how closely they match expectations and may experience great pressure to live up to specific expectatio

ns. Hence, cloning might constrict a childs future and might compromise the ch
ilds freedom to make choices in life, to develop his or her talents and interes
ts, and to develop a unique identity.
Others do not find these concerns persu
asive, because having identical genes as another person need not restrict life
choices or compromise individual identity. Identical twins are genetically ide
ntical and look almost alike at any point in time, yet regard themselves and ar
e regarded by their families as unique persons who make their own choices in li
fe. In response, opponents of cloning point out that no one chose to create th
e twin and there was no pre-existing person whose qualities were to be duplicat
ed. For these reasons, opponents believe that the twin analogy does not apply
to cloning.
Claims that children born after cloning through nuclear transfer
from somatic cells would not be valued for their own sake
The intention of usin
g nuclear transfer cloning in many scenarios is to produce a child with specifi
c preselected characteristics. The resulting child may be intended to be like
a beloved child that is dying, to be a genetic match for another child needing
an organ transplant, or to express scientific or musical talent. Some critics
predict that catalogues of people willing to be cloned would appear, allowing p
arents to select a template based on characteristics of the donor. As explaine
d in Chapter 00 (Science), this intention to duplicate an existing person is ba
sed on a misunderstanding of the degree to which gens determine the individual.
serious scientific misunderstandings and fallacious ideas of genetic determini
sm.
Critics of nuclear transfer cloning fear that parents who hope to specify
the childs characteristics -- no matter how scientifically incorrect these hop
es -- might value the children by how closely they match the preselected specif
ications. Indeed, because such parental hopes are futile, their disappointment
may be greater. According to critics, objects may be evaluated by whether the
y meet certain standards, but children should be loved unconditionally and for
their own sake, not because they match a preselected phenotype. Children who f
eel they have not met parental expectations may lack a sense of security and se
lf-confidence.
In some widely discussed scenarios, nuclear transfer cloning w
ould harm children by treating them as less then full persons. Such scenarios
include killing a clone to harvest a heart for transplantation or treating a cl
one as a slave. The Commission believes strongly that should any child born as
a result of cloning through nuclear transfer of somatic cells should be treate
d as a full person, like any other child. It would be immoral as well as illeg
al to treat a child born through cloning as a source of vital organs or as a sl
ave.
Claims that children would be harmed by confused social relationships
Th
e status of the child arising from nuclear transfer of somatic cells may be unc
ertain. For some, the disparity between the childs genetic and social identity
threatens the stability of the family. Is the child who results from nuclear
transfer cloning the sibling or the child of its parents? The child or the gra
ndchild of its grandparents? From this perspective the childs psychological an
d social well-being are in doubt or even endangered. Ambiguity over parental r
oles may undermine the childs sense of identity. It may be harder for a child
to achieve independence from a parent who is also his or her twin.
Others are
NOT persuaded by these objections. Children born through assisted reproductiv

e technologies may also have complicated relationships to genetic, gestational, and rearing parents. Skeptics point out that there is no evidence that confusion over family roles has harmed children born through assisted reproductive technologies, although the question has not been widely studied.

The risks to women involved in cloning as oocyte donors or gestational mothers are unacceptable at present.

Harms may occur to the women involved as ooctye donors or gestational mothers as well as to the children born after nuclear transfer. The Commission unanimously agrees that [I have not heard this argument at any commission meeting and I have not agreed to it] Some people say it would be ethically unacceptable at the present time to subject oocyte donors and gestational mothers to the risks of hormonal manipulation for the purposes of generating children through nuclear transfer of somatic cells. The risks to these women are the same as the risks associated with in vitro fertilization and include short-term discomfort, ovarian hyperstimulation, and long-term risks of reduced fertility and ovarian cancer. Ethically, experimentation with human beings is unacceptable unless the risks are proportionate to the expected benefits. In the Dolly experiment, 277 attempts were required before successful cloning. In view of the low likelihood that cloning of children through nuclear transfer of somatic cells would be successful at present, the risks to women far outweigh the likely benefits of the experiment.

Alleged harms to important social values

Critics fear that nuclear transfer cloning from somatic cells would cause harms to social values as well as alleged harms to individual persons.

Alleged harms to values about children and parenting

Critics ask us to imagine a world in which cloning through nuclear transfer from a somatic cell were permitted. What kind of people, parents, and children would we become in such a world? Opponents fear that cloning to create children may disrupt the interconnected web of social values, practices, and institutions that support the healthy growth of children. Attempts to determine the characteristics of a child through the use of nuclear transfer cloning are doomed to failure because they assume incorrectly that the child is determined by the genes they rest on a discredited view of genetic determinism. But however misguided those attempts, they even just the intention itself may still harm important social values. Critics fear that the use of nuclear transfer cloning might undermine the view that children should be encouraged to develop their own uniqueness as a person. In this view, the use of cloning might also encourage the undesirable view that children are to be valued according to how much they meet parental expectations, rather than loved for their own sake. In this way of looking at families and parenting, certain values are at the heart of those relationships, values such as love, nuturing, loyalty, and steadfastness. In contrast, a world in which cloning were permitted would might give implicit approval to vanity, narcissism, and avarice. To these critics, changes that undermine those deeply prized values should be avoided if possible. At a minimum, such undesirable changes should not be fostered by our public policies. Cloning to create children, to the extent that it disrupts those values, therefore ought to be discouraged.

Others are not persuaded by these objections. Skeptics point out that if strongly held moral values are in decline, there are likely many reasons, which would not be addressed by a

ban on cloning. Furthermore, skeptics argue that people can adapt to new tech
nologies. In their view, a child born after cloning can simply be loved and ac
cepted like any other child.
Alleged violations of justice and fairness
Criti
cs raise three objections to cloning based on justice. The first is an argumen
t from justice as equal opportunity: Creating a child through nuclear transfer
cloning would be wrong because it would be more available to the wealthy and po
werful than to the poor and powerless. Any advantages resulting from cloning w
ould exacerbate inequalities already present in the U.S. Even if there are no
actual benefits of creating a child through nuclear transfer cloning, because o
f the interplay of genetics, education, and environment in human behavior, the
mere perception of benefit may confer an advantage in terms of confidence or ex
pectations of others. The second argument considers the scarcity of resources.
The generation of children through nuclear transfer would divert scarce resou
rces, including money and the skills of researchers and clinicians, from more p
ressing social and medical needs. These considerations about allocation of res
ources are particularly pertinent if public funds would be involved. A third c
oncern rests on justice as equality of human worth. Critics fear that the abil
ity to select childrens appearance and physiogomy through nuclear transfer from
a somatic cell would lead to discrimination against persons who differ from th
e predominant social views of what appearance is desirable. Some fear that hum
an cloning would offer an opportunity to practice eugenics or heighten discrimi
nation based on race.
Historically there has been enormous strife based on ra
cial and ethnic differences, and critics believe that creating children through
nuclear transfer cloning will aggravate such divisions.

Arguments that clon
ing of children through nuclear transfer of somatic cells is wrong in itself.

Critics of cloning object that it is morally unacceptable, not only because it
produces harms but also because it is wrong in and of itself. That is, critic
s suggest that cloning violates fundamental moral principles, in ways we next d
iscuss.
Claims that cloning children through nuclear transfer from somatic ce
lls treats violates human dignity
Critics fear that parents who use such nuclea
r transfer cloning are likely to have very specific expectations for their chil
d, even though those expectations are based on a mistaken view of genetic deter
minism. Thus children resulting from cloning may be valued for meeting predete
rmined specifications, not loved for their own sake. In this view, cloning vio
lates the dignity of children, by treating them like products and objects rathe
r than as human beings. Critics believe that viewing children in this way is m
orally wrong, even if it caused no psychological harms to the children. Howeve
r, others are not persuaded by this line of argument. In their view, whatever
their original expectations, parents are likely to love their children for thei
r own sake and cherish their individuality.
In certain situations, the clonin
g of creation of children through nuclear transfer from of somatic cells would
undermine human dignity to such a degree that it would indeed be morally unacce
ptable. One ethically unacceptable scenario is using children created through
nuclear transplantation solely as the means to achive someone elses goals, rath
er than respecting them as ends in themselves. An example is destroying a clon

ed child produced though nuclear transfer after birth in order to achieve such goals as providing a heart for transplantation. A second unethical situation would be commercialization of nuclear transfer cloning, with different prices paid to different persons willing to donate nuclei be cloned, according to their perceived desirability. Buying and selling different combinations of genes nuclei and thus gene sets from various individuals [avoid different conbinations as it implies can choose the conbination when in fact it is fixed] that would make having children tantamount to purchasing commodities and thereby violate human dignity.

Claims that cloning may violate informed consent

Generation of a child through nuclear transfer cloning would be ethically unacceptable if it occurred without informed consent of the person whose DNA was used. Lack of consent would undermine human dignity because it violates a persons bodily integrity, autonomy, and freedom not to reproduce. Using a persons nucleus as a donor for nuclear transfer cloning Cloning without consent wrongs a person even if her or she is not physically harmed in any way. (In this line of thinking, it would also be improper to use a child as a nuclear donor clone children. Children are not capable of giving informed consent. Even if their parents consent to having them cloned, the child may wronged by becoming a parent without having agreed to do so.)

Claims that cloning violates moral boundaries

Critics assert that cloning tempts human beings to transgress moral boundaries that should not be crossed and to grasp for powers that are properly outside human control. Ancient Greek literature and many Biblical interpretations emphasize that human beings are between animals and the divine -- neither driven by instinct nor omnipotent over nature. In this view, respecting limits is to respect this place of mankind in the universe and to ensure that technology is used in morally acceptable ways and not allowed to run out of control. This view need not be tied to a particular religious doctrine, view of God, or even a belief in God. However, these objections are often expressed in religious terms: cloning tempts human beings to seek immortality, usurps the role of God, or violates divine commands. Many religious traditions consider procreation divinely ordained because it symbolizes the limits of any individual human being, the inevitability of death, and the necessity of human interdependence and cooperation. Two individuals must join to procreate; neither alone is sufficient. Parents are awed that their child is both similar to and different from each of them, in unpredictable ways. Such wonder reinforces the need for human beings to be humble and to recognize their limitations.

Ethical arguments offered to support acts of cloning of children through nuclear transfer of somatic cells.

The following sections examine the moral arguments offered in favor of nuclear transfer cloning, first examining the alleged benefits of cloning to individuals and to important social values and subsequently rights-based arguments for cloning.

Arguments that cloning of children through nuclear transfer of somatic cells results in beneficial consequences.

Some people argue that generation of a child through nuclear transfer cloning is ethically acceptable in some circumstances because it leads to benefits for individuals or for society as a whole.

Claims

that cloning could benefit to a person with a fatal illness.
In some cases,
cloning may offer the only hope of curing a fatal illness. Suppose that a two-year old boy develops aplastic anemia, a disease in which the body fails to produce blood cells. This condition is fatal, but the child can be kept alive for months with transfusions and treatment for complications such as infection. The most effective treatment is bone marrow transplantation. Suppose, however, that no donor can be found who matches the sick child, either among the childs relatives or in a bone marrow registry.
In similar situations, parents have tried to conceive another child, hoping that the new child will be a match for the older sibling. Suppose, however, that in this case the parents are now unable to conceive. Cloning offers the only possibility of saving the childs life.
The parents are determined that they will love the new child for its own sake, even though he will also serve as a bone marrow donor for his brother. The new child will not suffer any serious or permanent physical harm from serving as a bone marrow donor. In this hypothetical case, the parents are motivated to save the life of their son. They are trying to replicate the genes that control transplant rejection. They do not intend to duplicate other characteristics of the son. Because the two children will be close in age, the younger son would likely face few expectations to duplicate the characteristics of his older brother. Admittedly, the family relationships after transplantation may be complicated. However, the parents believe the possibility of such complications is worth the opportunity to save their sons life.
Some members of the Commission believed such a situation justified cloning and avoided many objections to cloning. This scenario appears to reinforce important shared values regarding helping, compassion, altruism, and sacrifice for family members. Even those members who regarded cloning as unacceptable in all cases were sympathetic to the plight of the child and the wishes of the parents in such a tragic situation.
Claims that cloning would benefit the child who will be born.
Some proponents
argue that the generation of a child through nuclear transfer cloning can be a net benefit to the child. This argument takes two forms. One argument builds on the view that genetics has some effect on a persons characteristics and accomplishments. While Even if they reject rejecting a rigid view of genetic determinism, some parents may simply want to take advantage of whatever propensities genetics may confer. Realizing that the complex characteristics actual phenotype of the child will depend on the interaction of genetics with environment and education, the parents may nonetheless seek to determine some aspects of the childs makeup give the child a good start in life through selecting a genotype through nuclear transfer cloning. For example if one parent were a carrier for a potentially serious genetic disease, the parents might choose to not pass on that gene and thus give their child what they perceive as a better chance in life. Such parents may, after considerable soul searching, conclude that they will be able to refrain from excessive attempts to control the child and love the child for its own sake, whether or not it meets their hopes. In this view, a decision to use nuclear transfer cloning might benefit the child and would not harm him or her if the parents indeed are flexible and moderate. In rebuttal, critics question whether parents will actually be able to moderate their expectations about the child born after cloning and to refrain from trying to mold the child to conform to their expectations.
Another form of argument argument
compares existence, even with substantial impairments, with non-existence. Pro

ponents conclude that even a severely constrained existence is better than none at all, and that therefore cloning, even though it resulted in grievous harm to the child, nevertheless is as a net benefit to that child. Such reasoning has been criticized on several grounds. First, it makes the wrong comparison. Rather than comparing existence with non-existence, we ought to compare the choice to bring a child into the world with substantial burdens with the alternative of bringing a child into the world without those same burdens. If a child could be conceived without the risks associated with cloning, then that alternative would count as a strong ethical reason against cloning. The second critique of this argument claims that it misses the point and does not address the concerns about harm to children born of the procedure. A third rebuttal is that this argument is unacceptable because it would excuse any actions or decisions by the parents, even those that resulted in serious, avoidable harms to the child who was born.

Claims that cloning would benefit the parents.

Some have argued that in some scenarios the parents would benefit from cloning. For example, an infertile woman whose husband and only child are near death after an automobile accident seeks to clone the child. In such situations, the intention may not be to replicate the existing person but to have some genetic link to offspring. The motives of the people seeking cloning in such tragic scenarios evoke sympathy. However, others question whether cloning will be effective in achieving the parents goals. Even if cloning might benefit individual parents, some question whether these benefits outweigh the alleged harms to social values discussed previously. These critics question whether such dramatic but unusual cases should be the basis for public policies regarding cloning.

(I still feel that the section below is not necessary, we state in the introduction that this is science fiction, not realit. I do not see the use in discussing this issue in detail as is is discussed here)

Claims that cloning would benefit society by reproducing an exemplary individual

Some suggest that society would benefit if the remarkable achievements of Einstein, Madame Curie, Mahatma Gandhi, or Mother Theresa could be replicated through generating children containing the genes of tehse people. However, this suggestion rests on false assumptions about role of genetics in determining complex human traits. Having the genes of Madame Curie woiuld not generate another Madame Curie. Individual identity is the result of complex interactions between genes and environment during the development of a child.

Some individuals may be relucatant to abandon their faith in genetic determinism. For them, it may be useful to point out other objections to efforts to clone exemplary persons, however scientficially misconceived. If we were to try to replicate exemplary individuals, who should be cloned? While many Americans might agree that it would be desirable to replicate a great scientist or a great humanitarian, would there be agreement that society would benefit if an athlete or a movie star were cloned? Even assuming we could decide which exemplary individuals should be cloned, there is no way to restrict cloning to persons whom society deems to be exemplary. Anyone who can pay for the procedure would be able to clone anyone they deem worth cloning.

Arguments based on moral rights.

Other arguments in favor of cloning children through
nuclear transfer claim that people have a moral right to use cloning. This al
leged right can be characterized in various ways.
Claims of a moral right to
make decisions about having children free from government interference.
Decis
ions to choose a spouse or partner and to have children through coital reproduc
tion are intimate personal decisions. Many people support a right to make such
decisions free of government interference. Such a moral right has been claime
d to include the right to marry, the right to marital privacy, the right to con
traception, the right to abortion, and the right to be free of forced steriliza
tion by the state. Some argue that people also have a moral right to use assis
ted reproductive technologies or to avoid serious genetic anomalies through pre
natal testing. Proponents of cloning claim that there is a similar right to us
e this technique.
In some circumstances, a person or couple may want to repro
duce by using nuclear transfer cloning. For some infertile couples, cloning ma
y be the only means for them to have a child that has a genetic link to one of
them. Genetic lineage may be particularly important, for example to an inferti
le person whose relatives were all killed in the Holocaust. In these circumsta
nces, the options of adoption or sperm or egg donation may seem undesirable.
For other couples, cloning may offer an opportunity to have genetically related
offspring who are free of a serious genetic illness. For instance, a couple m
ay both be carriers for Tay Sachs disease. They have a 25% chance of conceivin
g a child with a genetic illness that is usually fatal within one or two years.
Dave Cox, Arturo Brito can you comment on the clinical prognosis here? Do we
need a better example? Furthermore, suppose the couple is opposed to pre-impl
antation genetic diagnosis or selective abortion after prenatal genetic testing
. They may wish to be spared the anguish of terminating a pregnancy, or they m
ay be morally opposed to abortion under these circumstances. Furthermore, the
couple may reject the option of sperm or egg donation from someone who is not a
Tay Sachs carrier. In these circumstances, cloning may be the only means to a
chieve their reproductive goals.
Proponents of a right to make decisions abou
t having children may believe that people may exercise that right even if other
s think they are wrong or misguided. In the extreme, proponents believe that p
eople should have a right to make decisions based on views of genetic determini
sm that scientific experts believe are mistaken.
However, many people deny th
at there is a right to cloning. Critics argue that cloning through nuclear tra
nsfer from a somatic cell is essentially different from procreation or reproduc
tion. In their view, cloning can be distinguished clearly from coital reproduc
tion or assisted reproductive technologies because passes on all the genes of o
ne parent and thus does not involve equal genetic input from a male and female
progenitor. Furthermore, critics point out that policies that restrict or proh
ibit creation of a child through nuclear transplantation would not implicate an
y rights that are strongly recognized, such as the right to marry or have acces
s to contraception.
Claims of a moral right to rear children.
In the U.S.,
parents have the freedom to raise their children according to their values and
aspirations, without government interference. Moreover, it is considered appro
priate and morally desirable for parents to rear their children to try to meet
certain expectations. In this line of argument, parents should be free to try

to have a child with a specific set of genes, if they hope that this will give the child a predisposition to develop in certain ways.

Critics point out that parental rights are not absolute and may be restricted to protect the best interests of the child or important social values. Critics believe that the alleged harms of cloning, discussed previously in the Chapter, justify restriction on parental rights.

Claims of a moral right to free scientific inquiry

Permitting free scientific inquiry shows respect for human achievement and flourishing. Allowing researchers to advance scientific knowledge may also lead to beneficial applications. However, scientific inquiry must respect other ethical values. For example, experimentation with human subjects is regulated by society, and there are several precedents for moratoria or bans on certain types of biomedical research out of concern for health, safety, or human dignity.

Framework for moral deliberation about public polices regarding cloning of children through nuclear transfer of somatic cells.

In this section we first discuss the differences between the ethical analysis of individual acts and ethical analysis of public policies. Subsequently we develop a framework for moral deliberation about public policies. Finally, we indicate what ethical considerations the Commission believes should guide public policy regarding cloning of children through nuclear transfer of somatic cells.

Moral deliberation about public policies differs from moral deliberation about individual actions

Moral deliberation about public policy to allow, prohibit or regulate generation of children through nuclear transfer cloning differs from moral reasoning about individual cases of cloning. When individuals make moral judgments, they may rely on many sources of moral wisdom and knowledge, including their religious faith and moral intuitions. People will use their understandings of morality to decide what they should and should not do, as well as judge the actions of others.

In moral discourse about public policy, we try to provide reasons that will persuade our fellow citizens. In deciding upon public policy, we must balance respect for moral beliefs that may be held by a minority, with moral considerations that are broadly accepted by the American people. Generally moral convictions can be formulated in ways that most people can understand and reflect upon. We have tried throughout this report both to respect moral beliefs in their original form, and also to reframe them if necessary in order to make them more accessible.

Some moral considerations will have more weight in public policy debate than in judgments about individual cases. The burdens of enforcing public policies must be considered. It is extremely intrusive to monitor reproductive decisions by individuals and couples. This has several policy implications. First, it is impractical to have a policy that allows some reasons for cloning, while prohibiting others, even though we make such judgments privately about individual actions. On the policy level, attempts to distinguish acceptable from unacceptable reasons will be intrusive and will lead people to misrepresent their true reasons to fit the acceptable criteria. Second, strict enforcement of restrictions or bans on cloning of children may be burdensome or ineffective. Some people fear that establishing policies that cannot be consistently enforced

invites hypocrisy, cynicism about the law, and selective or unfair enforcement. Third, the likelihood that a prohibition will be violated is no reason to eli minate it. For example, violent crimes like murder continue to be perpetrated, yet no one argues that laws against murder should not be enacted. Finally, an d most important, because the Commission strongly believes that generation of c hildren through nuclear transfer from somatic cells would be unethical at this time because of unacceptable physical risks, public policy should be crafted th at provides a strong deterrent to even a single attempt of such cloning.

Ethi cal issues regarding research on human subjects also need to be considered in p olicy discussions. If generation of children through nuclear transfer of somat ic cells were ever attempted, it would be such a radical departure from usual c linical practice that it would need to be considered research. Informed consen t would be required from donor of transferred nucleus, oocyte donor, and gestat ional mother. Indeed, informed consent for such cloning would need to be stric ter than usual in clinical research. Several questions of research ethics woul d need to be resolved before cloining could be considered: What level of risk should be permitted when research is carried out on an embryo that will be impl anted, carried to term, and become a child? What level of oversight should be applied to such innovative research? Is approval by a local IRB sufficient, or should stricter review from a national committee with more expertise be requir ed?

Finally, pragmatic considerations may carry great weight in determining p ublic policies. Widespread, strong opposition to a practice after full elabora tion of opposing views, education about the scientific aspects, and deliberatio n carries great weight in policy decisions. In a democracy, public opinion abo ut generation of children through nuclear transfer cloning is one indication of what arguments and reasons are persuasive. Furthermore, opponents of a contro versial policy may link it to other issues in the political process; continued advocacy of that policy may lead overall to more harm than good, if other desir able policies are thwarted. For example, opponents of generation of children t hrough nuclear transfer cloning might link a ban on cloning to continued public support for unrelated basic scientific and clinical research.

Framework fo r moral deliberation about public polices.

The Commission was asked to consid er whether public policy should permit, regulate, or prohibit generation of chi ldren through nuclear transfer cloning from a somatic cell. In the U.S., gover nmental policies that prohibit or regulate human actions require justification because of a general presumption against governmental interference in individua l activities. Obviously, this presumption can be rebutted under various circum stances for a variety of reasons. Governmental interference may be warranted, for example, to prevent individuals from harming others and to protect importan t social institutions and values. Many critics of generation of children throu gh nuclear transfer cloning are concerned that this initial presumption of no i nterference with individual actions will lead to unwise policies regarding clon ing. Indirect and long-term harms may be discounted, because they are difficul t to detect or measure.

There is no easy way to determine when and which gove rnmental interventions are warranted. No algorithm clearly indicates whether t he moral arguments for governmental interventions in a particular situation are stronger than the moral arguments against such interventions. Instead, we mus t engage in moral discourse, debate, and argument in a process of public delibe

ration. Closure must be reached, and decisions made, even if there is no conse
nsus.
Moral deliberation about governmental policies can only proceed by crit
ically examining (1) how to characterize the reasons why some people might clon
e themselves or others and the moral values that might be threatened by such cl
oning, and (2) how much weight to assign to these different interests and value
s.
There is a close connection between how we characterize various interests
and values and how much weight we assign to them. For instance, in our society
, decisions about procreation are generally shielded from governmental interven
tion. Much of the argument about whether to allow or prohibit cloning of child
ren may thus depend on whether genetic replication through cloning falls within
the sphere of reproductive or procreative freedom. The issue is whether gener
ation of children through nuclear transfer cloning is similar, in morally relev
ant ways, to reproduction or procreation, with or without technological assista
nce. However, even if society recognizes and assigns considerable weight to pr
ocreative freedom, it is not absolute. It may be justifiably overridden or out
weighed in some circumstances in order to protect other important moral values.
The difficult task is to determine when those conditions are met.
Our socie
ty has only just begun to reflect seriously on the possibility of generation of
children through nuclear transfer cloning and its implications -- it was hard
to sustain serious moral reflection when human cloning was deemed possible only
in science fiction or in the very distant future. It may premature to come to
closure on some issues because so little time has been devoted to the issue.
Our society will need to continue to reflect on the moral issues surrounding hu
man cloning in order to formulate defensible policies as the science develops.
One goal of this chapter is to help build a framework for sustained moral refl
ection and deliberation.

Which ethical considerations should guide public po
lices regarding generation of children through nuclear transfer cloning from so
matic cells.
We now discuss which ethical considerations should guide public
regarding cloning of children using nuclear transfer from somatic cells. We n
eed to answer a series of three questions.
The first question is how strong a
re the objections to a policy allowing generation of children through nuclear t
ransfer cloning. In the context of public policy, we need to reconsider the et
hical concerns discussed previously regarding individual acts of cloning.
The
Commissioners strongly agree that the unacceptable risks of physical harms to
the child and to the women undergoing oocyte donation and gestation justify a m
oratorium or ban on such cloning at the present time. Indeed, these possible p
hysical risks are currently so unacceptable that the Commission believes public
policy must offer a strong deterrent to even a single attempt at such nuclear
transfer cloning.
If we consider whether a policy permitting such nuclear tra
nsfer cloning might ever be acceptable at some future time, deliberations are m
ore controversial. Let us assume for the sake of argument that research on nuc
lear transfer cloning of animals suggests that the risk of using such technique
s on human beings is comparable to accepted risks of assisted reproductive tech
nologies. Under this assumption, are there moral concerns that would justify a
public policy prohibiting cloning?

On this question the Commission was divid
ed. Some Commissioners were persuaded that various of the harms and wrongs des
cribed earlier in this chapter were ethically compelling, and would be decisive
reasons never to permit nuclear transfer cloning. Other Commissioners were le
ss certain about the significance of the objections, and were unwilling to conc
lude that nuclear transfer cloning would be ethically impermissible, if and whe
n the risks could be shown to be minimal. A comparable range of views is refle
cted in the testimony, letters, and commissioned papers we have reviewed.
Peopl
es views on nuclear transfer cloning cannot be separated from their world view,
a web of values regarding human nature, families, and the good society. There
are several contrasting positions. One view holds that moral attitudes toward
the challenges posed by modern biology -- of which nuclear transfer cloning is
only one example -- should be rooted in traditional values regarding life, int
erpersonal relations, the family, and the natural order. This position, while
evolving to remain consistent with a changing world, is also based in deeply he
ld conceptions about what is natural. These conceptions are believed to provid
e a bulwark against shifting trends or untried ideas. As an example are the vi
ews of many Roman Catholic and Protestant theologians about the need to engage
in reproduction within the context of what is natural and ordained (intercourse
within a monogamous, heterosexual marriage). A second view believes in the fl
exibility of social structures and the mutability of persons. In this perspect
ive, change is not merely something that happens in the face of events such as
nuclear transfer cloning, but desirable because of the potential for human impr
ovement or perfectibility. Yet a third view is a pragmatic perspective arising
from the acceptance of modern life. In this view, the social impact of scient
ific developments can be something to be absorbed into life -- lived around, on
e might say. Many technological innovations were feared at the onset as underm
ining traditional moral values, yet have been absorbed into modern culture. Th
ese conflicting views of the issues in cloning by nuclear transfer rest on fund
amentally different perspectives that have been in opposition for centuries.
The second question to address in moral deliberations about public policy is ho
w to weigh these objections and concerns against restrictions on the freedom of
individuals to make decisions about having children without government interfe
rence. Those who regard nuclear transfer cloning as a form of reproduction bel
ieve it should be strongly protected, like other forms of reproductive freedom.
On the other hand, those who regard nuclear transfer cloning as essentially d
ifferent from reproduction would grant it no more protection than other human a
ctions. Again, these differences cannot be decided at this time, and further d
eliberation is surely needed.
The third policy-relevant question is whether t
here are countervailing ethical considerations that favor a policy of allowing
creation of children through nuclear transfer of somatic cells. There are exce
ptional scenarios of cloning, as described previously, that evoke sympathy. Ho
wever, people disagree on whether these unusual situations outweigh the potenti
al harms of a policy allowing nuclear transfer cloning. The Commission believe
s that many arguments offered in support of nuclear transfer cloning, such as b
enefiting children and society by cloning exemplary individuals, are based on a
seriously mistaken belief that replicating a persons genes will lead to duplic
ation of the persons traits or accomplishments. Again, further public discussi
on is needed to clarify our understanding of how genes interact with environmen
t and education in shaping human behavior. The Commission believes that it is
essential that public deliberations be based on a sound science. As citizens,
we must understand not only how some newly discovered genes are strongly associ

ated with certain serious inherited diseases but also how complex human behavio
rs depend on much more than our genetic inheritance.

In summary, Commissione
rs reached several conclusions on ethical considerations to guide public policy
regarding generating children through nuclear transfer from somatic cells:
All
Commissioners agree that generating children through nuclear transfer from som
atic cells is unethical at this time because of insufficient evidence that it i
s effective and safe.
All Commissioners agree that even if concerns about saf
ety could be resolved, cloning should be prohibited in certain circumstances.
These include paying people to be cloned and cloning a person without his or he
r informed consent. Furthermore, the Commission agrees that any children born
after cloning need to be treated as full persons. They could not be used as sl
aves or killed as sources of organs for transplantation. ALTHOUGH WE DID NOT V
OTE ON THESE, ARE THEY NOT POINTS OF AGREEMENT? DOES ANYONE DISAGREE?? I WE S
HOULD TRY TO ARTICULATE ANY SITUATIONS IN WHICH WE BELIEVE CLONING WOULD BE WRO
NG EVEN IF SAFETY ISSUES ARE RESOLVED.
All Commissioners agreed that many sce
narios of cloning human beings through nuclear transfer from somatic cells were
based on the serious misconception that selecting a childs genetic makeup woul
d be equivalent to selecting the childs traits or accomplishments. A benefit o
f widespread discussion of cloning would be a clearer recognition that a person
s traits and achievements depend heavily on education, training, and the social
environment, as well as on genes.
Some Commissioners believe that cloning wo
uld always be unethical because it undermines important social values and cause
s harms to the child born after cloning. On the other hand, other Commissioner
s found that many objections to cloning were not persuasive because people were
likely to adapt to new reproductive technologies and because cloning was unlik
ely to be widespread.
Some Commissioners thought that certain individual acts
of cloning might be justified. However, no Commissioners believed that many s
cenarious proposed for cloning to be compelling (I do not understand what the i
ntension here is). Moreover, some scenarios seemed clearly unethical.
All C
ommissioners believe that deep public opposition to cloning through nuclear tra
nsfer from somatic cells should be given great weight, even though they might n
ot personally share all those concerns. Attempts to achieve a policy allowing
cloning may cause more overall harm than good, by putting at risk public suppor
t for important, unrelated scientific research.
All Commissioners agree on th
e need for further public deliberation on the serious moral concerns about clon
ing. As we proceeded in our work, we learned from listening to members of the
public who addressed us and from each other. Many important issues remain uncl
ear or unresolved, such as whether there is a moral right to freedom to make de
cisions about procreation that includes a right to cloning. The Commission bel
ieves that it is essential to try to understand the diverse reactions to clonin
g and the ethical arguments for and against various policies regarding cloning
human beings. Our work is only the beginning of moral deliberation about the i
mpact of this new technology. We urge that during the moratorium or ban on clo
ning, the public continue to discuss the ethical issues we have sketched in thi
s chapter.

Cloning of DNA sequences and cell lines.

The Commission was ch
arged with examining the ethical issues regarding cloning of human beings throu
gh nuclear transfer from somatic cells. However, because the term cloning is
used in various ways, it is important to comment briefly on other uses of the t
erm.

Cloning of DNA sequences and somatic? (YES) cell lines are well-establis
hed scientific techniques that are widely used in basic scientific research. T
hese techniques do not lead to embryos that have the potential to develop into
human beings. These research tools have already led to important new treatment
s, such as improved forms of insulin for the treatment of diabetes, vaccines ag
ainst hepatitis, new drugs for the treatment of heart attack and stroke (recomb
inant TPA), as well as better diagnostic tests for such conditions such as tube
rculosis and cystic fibrosis. Carol Greider, Steve Holtzman, and David Cox, ca
n we give some examples of clinical advances due to cell cloning? (Cell cloni
ng is used in recombinant DNA work thus the advances are the same) Further pro
gress in medical research will require continued use of these techniques, subje
ct to existing requirements for peer review for federal funding of research and
regulations about biosafety.

Cloning of animals, as in the Dolly experiment,
offers the promise of increasing our understanding of fundamental biologic pro
cesses, such as the growth, development, and differentiation of cells into spec
ialized organs. Such knowledge also holds the promise of important medical adv
ances that will relieve human suffering, as discussed in Chapter 00, Scientific
Issues. Like all animal research, cloning of animals must be carried out in a
humane manner, in accordance with established federal and state regulations, a
nd with review and approval by institutional animal welfare committees.

In vi
ew of the important benefits of this research, the Commission strongly recommen
ds that research using cloning of DNA sequences, somatic cell lines, and animal
s continue to be permitted and receive federal funding, subject to existing reg
ulations and peer review for scientific merit. Any moratoria, regulations, or
prohibitions that might be proposed or enacted with regard to the cloning of hu
man beings or cloning research involving human embryos must not restrict clonin
g research on DNA sequences, cells, and animals.

Cloning research involving
human embryos.

Any research on cloning human beings through nuclear transfer
from somatic cells would involve human embryo research. The fusion of a human
somatic cell and a oocyte whose nucleus has been removed would produce a human
embryo, with the potential to be implanted in utero and develop to delivery.

Currently, federal funding for human embryo research is severely restricted. C
ongress has inserted restrictions on embryo research into the 1996 and 1997 App
ropriations Bills. Congress forbids human embryo research that leads to the de
struction or discarding of human embryos. Furthermore, research may not presen
t more than minimal risk to the embryo. In addition, a 1994 Presidential direc
tive forbids federal funding for the creation of human embryos expressly for th
e purpose of research. Although federal support for human embryo research is h
eavily restricted, there are few restrictions of human embryo research carried
out in the private sector, using nonfederal funds.

From a scientific viewpoin
t, progress in understanding molecular genetics and cellular differentiation cu

rrently can proceed through research using animal cells, human somatic cells, a
nd animals. Far more animal research would be required before promising therap
eutic ideas, such as embryonic stem cell transplantation for leukemia, liver fa
ilure, or diabetes, could be considered in humans. Thus cloning raises no pres
sing scientific reason to reconsider current restrictions on federal funding fo
r human embryo research.

//

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RsRST3WU[[^^ccdfe\efyqh` 0$ffhmJno2uOyz}}}~?TLMp'kc`xxxnfaYY "*r\h
CefZ3C
||ww &p@P ! -
.1! @ uy=/Bxd "Science is close to crossing some horr
endous boundaries" Leon Kass in Time Magazine March 10, 1997
Carol Greider.New
Century Schlbk========== END ATTACHMENT 1 ==========

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: greider@cshl.org (greider@cshl.org [UNKNOWN])

CREATION DATE/TIME:25-MAY-1997 21:23:42.00

SUBJECT: Re: Science Chap Edits

TO: nbac-members@lists.Princeton.EDU (nbac-members@lists.Princeton.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
NBACers:

I thinks that Steve's edits to the science section are very helpful. They help make the wording more precise.

The only thing among all the changes that I disagree with is the suggestion that we removes the papagraph that reads:

"Apart from the fact that embryonic stem cell lines have not yet been produced from farm animals, the other argument for using nuclear transfer to introduce germ line genetic alterations in farm animals is that it avoids one generation of breeding from the initial chimeric animals. This is an important time and cost saving factor in farm animals with long generation times and small litter size. This factor, however, might not be as important as once thought. In mice, it turns out, embryonic stem cells can also be used to generate cloned animals carrying gene alterations directly without the initial generation of chimeric animals....."

Although it may seem technical, for those who did not know about this, and are interested in the details, (and paying attention) it is an important point.

Thanks again for your detailed comments Steve. I do not have the electronic document, so it is up to Kathi and Harold if they want these changes made.

Carol

****
Carol Greider, Ph.D.
Cold Spring Harbor Laboratory
P.O. Box 100
Cold Spring Harbor, NY 11724

Phone: (516) 367-8808
Fax: (516) 367-8815
E-mail: greider@cshl.org
****

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tmazzaschi@aamc.org (Tmazzaschi@aamc.org [UNKNOWN])

CREATION DATE/TIME: 3-AUG-1997 17:22:15.00

SUBJECT: Adhoc: Varmus Denies CellPro Petition

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
NIH Director Harold Varmus this afternoon announced that he has denied the petition of CellPro, Inc. that the NIH initiate "march-in" procedures under the Bayh-Dole Act. The NIH release on Dr. Varmus's decision follows.

Tony Mazzaschi
AAMC

NIH Decision Regarding Petition from CellPro, Inc.

NIH Director Harold Varmus, M.D., today denied the petition of CellPro, Inc. (CellPro) that the NIH initiate "march-in" procedures under the Bayh-Dole Act in order to give CellPro a license to certain patents owned by the Johns Hopkins University and licensed to Baxter Healthcare Corporation (Baxter).

CellPro asserted that march-in was necessary to alleviate health needs that arise because a Federal District Court found the stem cell separation device developed by CellPro to infringe the patents. The Court has issued an order in that case allowing CellPro to keep its product on the market until an alternative is approved by the Food and Drug Administration and made available for sale.

Dr. Varmus concluded that the initiation of march-in procedures is not warranted based on the available information, but that the NIH will continue to monitor the situation until a comparable alternative product becomes available for sale in the United States. Although the petition was originally sent to DHHS Secretary Donna Shalala, the authority for march-in is delegated to the head of the funding agency, in this case, Dr. Varmus at the NIH.

"The patient care implications of this matter were our first priority and concern," said Dr. Varmus. "Our review indicated that patient needs would be met as long as one or the other cell separation device is available to people in treatment or clinical research programs. Since both devices are currently available under the terms of the Court Order, I do not believe march-in proceedings are warranted." Dr. Varmus added, "The NIH will continue to follow the situation to ensure that patient access to this tec hnology is not compromised."

The NIH recognizes that its decision today will not resolve the legal dispute between CellPro and Baxter, which has been the subject of complex

patent litigation. It is the position of the NIH that these companies have full power and authority to resolve this dispute on their own. The NIH has encouraged and will continue to encourage them to negotiate a resolution.

For more information, please read the accompanying backgrounder at (http://www.nih.gov/news/pr/aug97/niha-01.htm). The full text of the determination is available via the Internet at (http://www.nih.gov/news/pr/aug97/nihb-01.htm) or through the NIH Office of Communications at (301) 496-8740.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: racharo@facstaff.wisc.edu (racharo@facstaff.wisc.edu [UNKNOWN])

CREATION DATE/TIME:10-FEB-1998 13:37:52.00

SUBJECT: Administration's position on S.1601

TO: nbac-members@lists.Princeton.EDU (nbac-members@lists.Princeton.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
>From: "Ellis, Gary" <ellisg@od6100m1.od.nih.gov>
>To: "'r. alta charo'" <racharo@facstaff.wisc.edu>
>Subject: Administration's position on S.1601
>Date: Tue, 10 Feb 1998 11:23:44 -0500
>X-Mailer: Internet Mail Service (5.5.1960.3)
>
>The Feb. 9, 1998 Congressional record contains a message from the
>Administration regarding S. 1601...
>
>
>S. 1601--HUMAN CLONING PROHIBITION ACT
>
>On June 9, 1997, the President transmitted to Congress legislation
making it
>illegal for anyone to
>create a human being through cloning. The President believes that
using
>somatic cell nuclear transfer
>cloning techniques to create a human being is untested, unsafe,
and morally
>unacceptable. The
>Administration, however, believes S. 1601, as introduced, is too
>far-reaching because it would
>prohibit important biomedical research aimed at preventing and
treating
>serious and life-threatening
>diseases. Therefore, the Administration would not support passage
of the
>bill in its current form. The
>Administration looks forward to working with the Congress to
address these
>concerns. Specifically,
>the Administration supports amendments to S. 1601 that would:
>
>Include a five-year sunset on the prohibition on human somatic
cell nuclear
>transfer technology. The
>sunset provision would ensure a continuing examination of the
risks and
>benefits of this, while being
>free from the concern that someone will use it prematurely.

>
>Permit somatic cell nuclear transfer using human cells for the
purpose of
>developing stem cell
>(unspecialized cells capable of giving rise to specific cells and
tissue)
>technology to prevent and treat
>serious and life-threatening diseases and other medical conditions,
>including the treatment of cancer,
>diabetes, genetic diseases, and spinal cord injuries and for basic
research
>that could lead to such
>treatments.
>
>Strike the bill's criminal penalties and instead make any
property, real or
>personal, derived from or
>used to commit violations of the Act subject to forfeiture to the
United
>States.
>
>Strike the bill's provisions establishing a new Commission to
Promote a
>National Dialogue on
>Bioethics. The new Commission would needlessly duplicate the
mission of the
>President's National
>Bioethics Advisory Commission.
>
>The President's proposal, which in many ways is reflected in S. 1602
>sponsored by Senators
>Feinstein and Kennedy, would prohibit any attempt to create a
human being
>using somatic cell
>nuclear transfer, provide for further review of the ethical and
scientific
>issues associated with the use
>of somatic cell nuclear transfer, and protect important biomedical
research.
>
>

---

r. alta charo, j.d.
senior fellow, stanford center for biomedical ethics
701a welch road, suite 1005
palo alto, ca 94304
650-723-5760 (tel)
650-725-6131 (fax)
415-661-9987 (home)
racharo@facstaff.wisc.edu

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: robin alta charo <racharo@facstaff.wisc.edu> (robin alta charo <racharo@facstaff.wisc.edu> [UNKNOWN])

CREATION DATE/TIME:12-NOV-1998 09:49:30.00

SUBJECT: Re: FW: NEW YORK TIMES today!!!!!!!!!!!!!!!

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
fyi, neal first, here at univ of wisconsin, announced last january at a meeting in boston, that he had successfully mixed nuclei from one animal species with enucleated eggs from another species, working with a variety of non-human species. a key finding from his work is that normal cell division only goes on for a period of days (maybe a week?) before the cells begin to divide in an unorganized fashion. in other words, his hybridized egg/embryos did NOT have the potential to become fetuses of any species.

also fyi, with regard to the embryo stem cell technology developed by jamie thomson at univ of wisconsin, announced last week: our newly formed university bioethics advisory commission has advised the chancellor that stem cells be licensed to researchers at other universities only under certain conditions of use. one of those conditions is that the stem cells or their derivatives not be used with the intent to transfer them into a uterus for development into a human being.

thus, for neither of these technologies is there a risk that a baby could be born from the experiment.

At 09:20 11/12/98 -0500, you wrote:
>To consider with your morning coffee.
>
>Eric M. Meslin, Ph.D
>Executive Director
>National Bioethics Advisory Commission
>6100 Executive Blvd. Suite 5B01
>Rockville, Maryland 20892-7508
>Tel: (301) 402-4242
>Fax: (301) 480-6900
>Email: MeslinE@OD.NIH.GOV
>http://www.bioethics.gov

>
>-----Original Message-----
>From: Skirboll, Lana (OD)
>Sent: Thursday, November 12, 1998 5:22 AM
>To: 'EMARINCO@ascb.org'; Patterson, Amy (OD); Meslin, Eric (OD);
Emanuel,
>Ezekiel (CC); 'Howard Garrison'; 'mazzaschi,tony'; 'dkorn@aamc.org';
Knorr,
>Debra (OD); 'pberg@cmgm.stanford.edu'
>Subject: NEW YORK TIMES today!!!!!!!!!!!!!!!!
>Importance: High
>
>If you thought the news last week was replete with ethical problems, read
below.
>Now we have a combination of cloning, totipotent embryonic stem cells and
>human/animal chimeras! The founder of Geron, Michael West, now head of
Advanced
>Cell Technology, alleges he has created a totipotent embryonic cell line
using
>SCNT in which he transferred the nucleus from one of his own somatic cells
into
>an enucleated cow egg - now we have human-animal chimeras to deal with!
This has
>not been confirmed or even published, but Dr. West decided to begin the
public
>debate! Yikes!
>
>
>NEW YORK TIMES November 12, 1998
>
>
> Human Cells Revert to Embryo State, Scientists Assert
>
>
>
> By NICHOLAS WADE
>
> Venturing deep into uncharted realms of ethics and
medicine, a
>small biotechnology company
> said Wednesday that its scientists had for the first time
made
>human cells revert to the
> primordial, embryonic state from which all other cells develop,
by
>fusing them with cow eggs and
> creating a hybrid cell.
>
> The research comes from biologists who are well known in their
field,
>but has yet to be confirmed or
> even published in a scientific journal. Their company, Advanced
Cell
>Technology of Worcester,

> Mass., said the method could eventually be used to grow
replacement
>body tissues of any kind from
> a patient's own cells, sidestepping the increasing scarcity of
organs
>available for transplant and the
> problems of immune rejection.
>
> The technique is likely to concern and perplex ethicists
because it
>involves the creation of an
> embryonic cell that is part human and part cow, consisting of a
human
>cell's nucleus inside a cow egg
> whose own nucleus has been removed. The company said the hybrid
cell
>quickly became more
> human-like as the human nucleus took control and displaced cow
>proteins with human proteins.
> Creation of the embryonic cells is an important component of a
>strategy that in principle offers high
> medical benefits if it can overcome a doubtless high barrier to
public
>acceptance.
>
> The technique involves creating an embryo of uncertain moral
status,
>and one that crosses the barrier
> between humans and other species. Even though the hybrid is in
the
>form of cells, not a whole
> organism, the concept of half-human creatures arouses deeps
anxiety,
>as is evident from the
> unfriendly powers ascribed to werewolves, centaurs, mermaids,
>Minotaurs and other characters of
> myth and folklore.
>
> "Many people are going to be horrified by this scenario, others
will
>say 'So what?' " said Thomas
> Murray, director of the center for biomedical ethics at Case
Western
>Reserve University in
> Cleveland and a member of the National Bioethics Advisory
Commission.
>"This is the sort of thing
> that makes me very uncomfortable. I think we are likely to get a
very
>powerful reaction to it, and I
> would like for all of us to have a breathing space here to
articulate
>our moral concerns."
>

> Another serious uncertainty is the preliminary nature of the company's
>work. No article has yet been
> submitted for peer review and publication in a scientific journal, an
>essential touchstone of credibility.
> Scientists asked about the company's work said they would require much
>more proof before
> believing that human embryonic stem-like cells had been created as
>claimed, and some were
> skeptical the technique would work at all.
>
> The company said it had achieved the feat announced Wednesday with one
>cell three years ago.
> Michael West, Advanced Cell Technology's chief executive officer, said
>he was announcing the
> work done to date in order to test its public acceptability He said
>the company, which is privately
> held, was not planning to go public or raise money at this time but
>needed to decide whether to
> commit investment to development of the technique.
>
> Some scientists praised West's decision to make his work public but
>others are critical, saying he has
> invited an emotional public debate on a slender basis of fact.
>
> West is the founder of Geron, a biotechnology company that has had two
>spectacular successes this
> year in its research on aging. In January, the company developed a
>method for "immortalizing" human
> cells grown in the laboratory by making them leap the supposedly
>immutable barrier at which cells
> usually lapse into senescence. Last week, two university teams
>financed by Geron said they had
> isolated and cultivated human embryonic stem cells, the all-purpose
>cells from which the fetus
> develops. West lay the foundations for these developments by financing
>leading scientists in the two
> fields.
>
> Advanced Cell Technology, which West joined in October, has focused on
>cloning and genetically

> improving cows, a technology developed by James Robl and colleagues at
>the University of
> Massachusetts in Amherst. West said he hoped to use the technology to
>further the founding concept
> of Geron: delving into the mystery of human aging and sidestepping
>some of its processes.
>
> The company said work with human cells was performed in 1996 by Jose
>Cibelli, a colleague of
> Robl at the University of Massachusetts. Using 52 of his own cells,
>some of them white blood cells
> and others scraped from the inside of his cheek, Cibelli fused each
>one with a cow egg whose own
> nucleus and DNA had first been removed, the company said. Most failed
>to thrive but one embryo
> grew and divided five times, generating cells resembling embryonic
>stem cells. Cibelli and West say
> the method can be made more efficient with present technology.
>
> Considering this work was sufficient to describe an invention, Robl
>and Cibelli filed a patent
> application and then set the research aside to focus on the more
>immediately practical field of cow
> cloning. Only two others besides himself and Robl knew what had been
>done, Cibelli said. The
> patent has not yet been issued but West said he was confident of
>receiving "important intellectual
> property" in the field. He said he is making the hybrid cell technique
>public now "because I want to
> be very open and level with everyone. We need to get the ethicists to
>talk about it so as to
> encourage a rational response to these new technologies."
>
> Cibelli said he regarded any embryos obtained in this way as "not a
>separate individual, just a
> de-differentiated cell from a patient." Differentiation is the process
>whereby the all-purpose cells of
> the very early embryo, known as human embryonic stem cells, become
>committed to their roles as

> the various specialized tissues of the body. The process is
>irreversible in nature but egg cells
> apparently have the ability to de-differentiate, or reset to
default
>mode, the settings in a specialized
> cell's nucleus. This is presumably what happened in the
experiment
>reported in July when mice were
> cloned by transferring the nucleus of an adult mouse cell into
another
>mouse's egg cell.
>
> Cibelli, who trained as a veterinary doctor in Argentina, said
he
>believed that he and his colleagues
> "were the first to de-differentiate a human cell by nuclear
transfer."
>
>
> Asked if he was concerned about destroying, in principle, 52
potential
>twins of himself, he said, "I
> never thought about it, it's a good question. But if you use
your own
>cells to treat a disease you may
> have, you are not taking cells from another person selfishly."
>
> West and Cibelli said they had no intention of transferring the
>embryos to a uterus, a step they
> consider unethical and unsafe for it. The embryos would be
created
>solely for the purpose of tissue
> culture. "Any technology can be abused but once the public
understands
>how these cells can be used
> to treat any disease caused by loss or malfunction of cells,
from
>Parkinson's to diabetes to heart
> disease, the concerns will be overshadowed," West said.
>
> Whether or not West's prediction will be borne out depends on
two
>major sets of factors, the
> scientific validity of the proposed method and the ethical and
legal
>questions that related work has
> already raised.
>
> From discussions with scientists, ethicists and lawyers in the
past
>few days, several concerns have
> emerged.
>
> Scientists are particularly critical of the lack of supporting

>evidence accompanying Advanced Cell
> Technology's announcement, saying in essence the claim could be
true
>but there was no compelling
> reason yet to accept it. Even if the claim is valid, biologists
note a
>serious uncertainty relating to an
> important part of the cells known as the mitochondria,
components that
>produce the energy the cell
> needs and that are, in essence, the cell's batteries. If the
bovine
>mitochondria should prove
> incompatible with their humanized environment the cells will
not be
>viable.
>
> Ethicists believe the mixing of species is likely to trouble the
>public severely, at least at first. Lawyers
> who specialize in issues of human reproduction note that the
moral and
>legal status of the human
> embryo is undecided in American law, a fact pointed up by the
>isolation of the human embryonic
> stem cells announced last week. The new entity adds further
>complexity.
>
> If Advanced Cell Technology can produce viable hybrid cells,
those
>cells will offer a new route to
> grow tissue for transplant. This is the same goal held by the
>scientists who announced last week they
> had grown human embryonic stem cells in the laboratory. It is
widely
>accepted in principle that
> embryonic stem cells can be directed to develop into any desired
>tissue, with enormous potential for
> medicine, even though this has yet to be achieved in practice.
>
> West said the advantage of the Advanced Cell Technology method
was
>that embryonic cells derived
> from the patient being treated would generate entirely
compatible
>tissues. The two methods reported
> last week, by James Thomson of the University of Wisconsin and
John
>Gearhart of Johns Hopkins
> University, derive stem cells from human embryos or fetuses.
Tissues
>made from these cells would
> be incompatible with the patient, a problem that has yet to be
>resolved.
>

> In support of its claim, Advanced Cell Technology supplied a
patent
>application and a photograph
> taken of its embryonic cells under a microscope. The patent
>application describes how the cells are
> made but provides no proof that they possess the properties to
be
>expected of human embryonic
> stem cells. Robl said his laboratory was not set up to perform
the
>required tests at the time the hybrid
> cells were made.
>
> Shown the photograph of the hybrid cells, John Gearhart of Johns
>Hopkins University, author of one
> of the two methods reported last week, said that "they certainly
could
>be embryonic stem cells" but
> that no scientific journal would publish the result without
further
>proof. "It's not that I don't believe
> this biologically. I just think they could have given a little
bit
>more assurance as to what was done
> here."
>
> Roger Pedersen of the University of California at San Francisco,
who
>also works on human
> embryonic stem cells, said he doubted the hybrid cells would
last long
>enough to develop into useful
> tissue because of their cow-derived mitochondria.
>
> Mitochondria, former bacteria enslaved by cells eons ago, have
their
>own genes but operate in close
> cooperation with genes from the cell's nucleus.
>
> Pedersen cited a recent experiment showing that within the
>human-ape-monkey family, each species'
> mitochondria is subtly different, the more so the longer the
>evolutionary distance between the species
> in question. The mitochondria of chimpanzees and gorillas work
well
>enough in human cells but those
> of primate species that diverged more than 10 million years ago
from
>the human line, do not work.
>
> Because cows and humans last shared an ancestor so long ago, cow
>mitochondria are very unlikely
> to work well with a human nucleus, in Pedersen's view, and asmost of
>the mitochondria in the hybrid

> cells are contributed by the cow egg, the cells would probably
not
>remain viable for long. "It's hard
> to say this is a total sham, but I smell a sham here," he said.
>
> Citing the same data, Gearhart said the mitochondria in the
hybrid
>cell had clearly carried it through
> its first few divisions but might not sustain it in further
>development, unless the few human
> mitochondria that were also present somehow took over.
>
> Pedersen said Advanced Cell Technology should be held to a high
>standard of proof "because of
> what the implications are for upsetting people unnecessarily --
if you
>cry fire in a crowded auditorium
> you may be liable if it's a false alarm."
>
> The human embryonic stem cells announced last week have already
pushed
>against the frontiers of
> ethical acceptance. Experts in biomedical ethics say the public
is
>likely to be alarmed by the new
> technique, particularly because of the mingling of species.
Murray of
>Case Western Reserve
> University said that the hybrid embryo "escapes our usual
categories."
>When biologists first learned
> to transfer genes from one species to another, "The idea of
>human-animal hybrids was often raised as
> the kind of monstrosity that no morally perceptive person would
ever
>create," he said.
>
> "Even if it's only to create tissue, the minute you start mixing
>species you raise all kinds of red flags in
> people's minds," said Barnie Steinboch, a moral philosopher at
the
>State University of New York in
> Albany. But she noted that pig valves are now seen as acceptable
>replacements in human hearts.
>
> Rebecca Dresser, a law professor at Washington University in St.
>Louis, noted, as did several
> biologists, that distinctions between humans and other animals
are
>less clear in nature than they are in
> people's minds. "Biologically a lot of this research is showing
us
>similarities and the upshot in a
> hundred years may be that the lines between humans and

non-humans will
>be viewed as a little bit
> grayer," she said.
>
> A perplexing feature of the hybrid embryo is that it starts off
mostly
>bovine and then becomes mostly
> yet not entirely human. But some legal experts have no doubt
that it
>should be regarded from the
> start as a human embryo. "It doesn't matter that the
mitochondria come
>from a cow, it also has
> human mitochondria and so has all the potentials of a human
embryo,"
>said Lori Andrews of the
> Chicago-Kent College of Law in Chicago.
>
> "Once it's gone through that first division it has gone from
being a
>somatic cell to a thing with potential
> life," she said, referring to the ordinary specialized cells of
the
>human body. If transferred to a
> woman's uterus the embryos may or may not come to term, "but
under
>state laws it doesn't matter
> whether the fetus is going to be born or not - it doesn't make
them
>less human."
>
> The human body consists of 100 billion cells. Should embryos
created
>from them by the cow egg
> method be regarded as having special status when they can be
made so
>easily and plentifully? Ms.
> Andrews said that human embryos are not so hard to make the
usual way,
>and the fact that an
> embryo is easily made, by whatever means, is irrelevant to
arguments
>about its status.
>
> The moral status of the human embryo "is not clearly
established in
>U.S. law," Dresser said. The
> embryo can be regarded as mere property, as a person, or as
something
>in between but deserving of
> special respect. Congress, in banning the use of federal funds
for
>research on human embryos, has
> favored the view that they are in the category of people. But in

>custody battles over fertilized
> embryos, courts have favored the special respect status. Dresser
said
>the hybrid cells could be seen
> as somewhere between the property and special-respect status.
>
> The hybrid cells were made by Cibelli in Robl's laboratory in
the
>University of Massachusetts at
> Amherst. Michael Weinberg, executive secretary of the
university's
>human subjects committee, said
> the experiment was given administrative approval, without
review by
>the committee or any major
> discussion. Cibelli was using his own cells, not experimenting
on
>other people, and
> self-experimentation does not require special consent. "If
someone
>wants to inoculate themselves
> they can do that," Weinberg said.
>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME:13-NOV-1998 11:32:22.00

SUBJECT: FW: more on human/cow cell breakthrough

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Commissioners, et al.

You will all have seen this, by now.

Let me inform you that after discussions with Harold, he has decided that, if
asked by the administration, NBAC would be prepared to offer its assistance.
Should this occur (and it has not), I will share the request with you and discuss any potential action on our part.

Eric

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
6100 Executive Blvd. Suite 5B01
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Tel: (301) 402-4242
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Email: MeslinE@OD.NIH.GOV
http://www.bioethics.gov

-----Original Message-----
From: Hull, Randolph Everson (OD)
Sent: Friday, November 13, 1998 10:09 AM
To: Andrew Siegel; Deborah McCurry; Elisa Eiseman; elisa2; Emma Codrington;
Eric Meslin; Evadne Hammett; Feinstein, Emily; Freeman, Bill; Hull, Randolph
Everson; Hyatt-Knorr, Henrietta; LaShell Gaskins;
lpknowle@facstaff.wisc.edu;
Melissa Goldstein; Norris, Patricia; Quinlan, Margaret; Simon, Sean; Tanner,
Rob; Temp NBAC
Subject: more on human/cow cell breakthrough

Mass. Firm Says It Created Embryo Out of Human, Cow Cells

By Rick Weiss
Washington Post Staff Writer
Friday, November 13, 1998; Page A01

Scientists, ethicists and federal regulators scrambled yesterday to sort out the many controversial issues raised by a small biotechnology company's announcement that it had used cloning techniques to create an embryo out of human and cow cells.

The work, conducted in 1995 and 1996 at Advanced Cell Technology of Worcester, Mass., but not made public until yesterday, was part of an effort to make medically useful tissues but also appears to be the closest that anyone has come to cloning a human being.

Among the many questions raised by the revelation was whether the research broke a ban on the use of federal funds for embryo research; whether it bypassed Food and Drug Administration rules on research; and how the work passed muster with the ethics review board at the University of Massachusetts in Amherst, where the company-supported work was done.

Those and other uncertainties led several experts yesterday to call upon Congress and the White House to clarify the regulatory framework within which human embryo research and other high-tech human studies are conducted.

"We will be contacting the White House today to ask that the president have the National Bioethics Advisory Commission examine these issues," said Carl Feldbaum, president of the Biotechnology Industry Association, who said he was excited by the findings but was concerned by the lack of regulatory clarity.

The Worcester company produced one cloned human embryo - perhaps the first ever made - and performed the unprecedented cross-species hybridization of a human cell and a cow egg.

Michael West, president of the company, said in an interview yesterday that although the technique was very similar to that used to clone Dolly the sheep, he had no intention of cloning adult humans. Rather, the project's goal was to grow replacement cells and tissues for transplantion into people with

diseases.

West said he had recently reopened the files on the dormant experiment and concluded that it was largely successful. He was publicizing the findings, he said, because the company had the moral responsibility to get feedback from the public before going any further.

Several critics, however, said they suspected the company had made a business decision to ride a new wave of interest in cultured embryonic cells, spurred by recent promising reports published in scientific journals. In contrast to those recent studies, West's company has not submitted its findings for review and publication in a research journal. Instead it released its findings to the New York Times, which ran a report about it yesterday. That suggested to some that the company was primarily trying to position itself to make an an intellectual property claim on cell transplant technology.

"What do they have? They've got no publication, they've got nothing," said George Annas, a professor of health law at Boston University. "All they have is the opportunity to tag along with the other stem cells in the news. They're saying, 'Let's cash in.'"

West said the company's team had fused a human skin cell to a cow's egg whose genes had been removed. The fluids that remained in the gutted cow egg caused the genes in the human cell to revert to their primordial state, as though they were back in a developing human embryo. The fused cell divided several times, and microscopic examination indicated that some of the resulting cells resembled stem cells, which scientists hope to harness for medical purposes and for which the company has submitted a patent claim.

Other scientists disputed West's conclusions, however, saying the Worcester team never did the basic tests used to see if cells are really stem cells. West confirmed those tests were never done.

Roger A. Pedersen, a stem cell researcher at the University of California, San Francisco, said the company's claim of having isolated stem cells shocked him.

"One must be very circumspect about such a fanciful notion without good data to support it," he said.

Moreover, Pedersen and others said, experiments in other species have shown that hybrid embryos made from divergent species grow poorly and suffer many defects because of an incompatibility between the newly transferred genes (in this case human) and so-called mitochondrial genes that are left behind in the fluid of the gutted egg.

"There's a carefully choreographed dance between nuclear DNA and mitochondrial DNA," Pedersen said, saying he doubted the Massachusetts team's cells would have much medical value.

John Gearhart, who last week published a scientifically reviewed report showing he had isolated human embryonic stem cells from fetuses, agreed, saying the new report reminded him of the much ballyhooed and ultimately disproved claims of "cold fusion" earlier in this decade.

Experts also questioned the legal and ethical basis of the work. Congress has banned federal funding for human embryo research, and Gearhart, Pedersen and others work in labs from which federally purchased equipment has been scrupulously excluded.

West said the company's embryo work was done using only corporate funds, but officials at the University of Massachusetts said they were unaware that any of the labs in the building where the work was done had been specially cleared of all equipment purchased with federal grant money. "We don't have an NIH room and an NSF room and so on," said Michael Weinberg, special assistant to the vice chancellor for research. "Faculty members get funded and they go from room to room."

The role of the FDA also remained unclear yesterday. Acting FDA Commissioner Michael Friedman said that if the work was basic research then the company was under no obligation to get approval from the agency, but if it was done

with the
intention of developing a cellular therapy for use in humans then the company
should have filed for an Investigational New Drug application. With only a
newspaper report to describe what the team did, he said, it remained unclear to
him which category the work belonged in.

Others questioned how the university's institutional review board could approve
the species-mixing research. Weinberg, who heads that committee, said the group
only considered whether it posed a risk to the researcher who donated his skin
cells. But other experts said such committees are clearly required by federal
law to consider the full range of scientific and ethical issues raised by
proposed research. They said the committee's quick approval gives credence to a
recent federal report that called for a major overhaul of the nation's local
research review system.

"What this whole business shows is that we are in a regulatory nightmare," said
Glenn McGee, a professor of bioethics at the University of Pennsylvania. "It's
going to be impossible to state whether these things are really human, let alone
how to protect them."

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RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tony Mazzaschi <Tmazzaschi@aamc.org> (Tony Mazzaschi <Tmazzaschi@aamc.org> [UNKNOWN])

CREATION DATE/TIME:15-NOV-1998 09:58:06.00

SUBJECT: Adhoc: Clinton Requests NBAC Review of Stem-Cell Research Issues

TO: clinicalmail@aamcinfo.aamc.org (clinicalmail@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: basicmail@aamcinfo.aamc.org (basicmail@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: research-aamc@aamcinfo.aamc.org (research-aamc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: casmail@aamcinfo.aamc.org (casmail@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
According to Sunday*s NY Times, the President on Saturday wrote to the chair of the National Bioethics Advisory Commission asking that the panel review at its Tuesday meeting the ethic issues raised by embryonic stem-cell
research. The Times* article on the President*s request follows.

Tony Mazzaschi
AAMC

November 15, 1998

Effort to Make Part-Human, Part-Cow Cells Troubles Clinton

By NICHOLAS WADE

Saying that he is "deeply troubled" by the creation of part-human, part-cow embryonic stem cells, President Clinton has directed the National Bioethics Advisory Commission to consider the implications of the research at its meeting Tuesday in Miami and to report back to him "as soon as possible".

In a letter sent Saturday to the chairman of the commission, Harold Shapiro of Princeton University, Clinton also asked for a review of embryonic stem-cell research in general, including the all-human embryonic stem cells whose isolation was reported earlier this month. These cells -- the primordial, all-purpose cells from which all tissues of the body develop -- were derived from very early embryos or blastocysts and from tissues of aborted fetuses.

While the president signaled concern about the "mingling of human and non-human species," he was more positive about the all-human embryonic stem cell research, noting that it "may have real potential for treating such devastating illnesses as cancer, heart disease, diabetes and Parkinson's disease."

But he also stressed the ethical concerns raised by the research, telling the commission that he wanted a "thorough review, balancing all ethical and medical considerations."

The letter was sent after the president had consulted with the White House Domestic Policy Council and the president's science adviser, Neal Lane, "because he wanted the broadest views possible -- the policy people, medical ethicists, as well as the scientists," an administration official said.

A political issue that lies in the background of the commission's deliberations is the ban on federal financing of fetal research. The ban, imposed by Congress, has created the situation that university scientists, who mostly depend on federal money, cannot work on the human embryonic stem cells whereas the private sector may conduct whatever research it pleases.

A group of scientists and ethicists known as the Human Embryo Research Panel said in 1994 that research on human embryonic stem cells should be federally financed, provided that the cells were derived from excess pre-implantation embryos created for infertility treatments. This was the source of some of the human embryonic stem cells isolated earlier this month.

In response to the panel's report, Clinton said in December 1994, "I do not believe that federal funds should be used to support the creation of human embryos for research purposes." The statement did not rule out research on excess embryos created in infertility clinics but subsequent action by Congress banned all research in which a human embryo is destroyed.

Referring to this history, the president said in his letter Saturday that the ethical issues of human embryonic stem cell research had not diminished since his statement of 1994 but that the benefits had become less hypothetical.

Lane said the implications of human embryonic stem-cell research had been under review but news of the human-cow hybrid cells, reported last week, "clearly raised urgent ethical, medical and legal issues that the president wants addressed and that's why he asked for the commission to give it immediate attention."

Human embryonic stem cells can develop into any of the body's 210 types of cells, a process that happens naturally during fetal development. Biologists at Geron, the company that supported the research, hope to grow the cells in the laboratory and guide them to develop into heart cells, blood cells and other tissues.

The cells would then be injected into the patient and integrate with tissues under the control of local body signals.

In principle, the method could address a range of otherwise untreatable degenerative diseases, as well as relieving the severe shortage of organs available for conventional transplants.

Many serious technical problems remain to be resolved, including finding ways to guide the stem cells down desired paths of development and ways to prevent immune rejection.

The ethical problems are also important because of the source of the embryonic stem cells. In one case the cells came from excess pre-implantation embryos created in infertility treatments, and in the other
from aborted fetal tissue. Both sources were legal, but research using the first would have been ineligible for federal money.

The human-cow hybrid cell also complied with all laws, said Michael West, chief executive of Advanced Cell Technology of Worcester, Mass., the company
that supported the research. In the hybrid cell, the cow cell's nucleus is first removed and the cow proteins are expected to be rapidly replaced with human proteins as the human nucleus takes over the cell.

Although the mingling of species raises many questions, scientists at Advanced Cell Technology regard the operation as one in which the cow egg is
used simply to make the human cell's nucleus revert to its embryonic state. As the human cells can be provided by the patient himself, from blood or skin, there is no immune rejection when developed cells grown from his embryonic state cells are injected back into the body.

Advanced Cell Technology performed its cow-human hybrid experiment only once, three years ago, and took the study only to a very preliminary stage. Other scientists say more evidence is needed to verify whether embryonic stem-like cells were created.

West said he was announcing the research now to test its public acceptability before making further investments in the technique.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Sean Tipton <stipton@asrm.com> (Sean Tipton <stipton@asrm.com> [UNKNOWN])

CREATION DATE/TIME:30-NOV-1998 10:31:07.00

SUBJECT: Adhoc: Stem Cell Research

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
Disclaimer: The Ad Hoc Group has not taken a stance on stem cell research.

As many of you know, the Labor Health and Human Services subcommittee of the Senate Appopriations Committee is holding a hearing to discuss advances in stem cell research and their implications. The hearing is set for Wednesday Dec 2 at 9:30 am in Dirksen 192.

As recent studies have shown, the promises of dramatic therapies using stem cells may be closer than had been thought. It is vitally important that this work be allowed to progress.

Hopefully many of you are signing on to a letter being circulated by BIO urging that stem cell research be allowed to progress free of barriers that would impede progress.

Unfortunately there are those who would oppose stem cell research in order to make larger political points. I hope the research community can send them a message that this work is important, and that we will work to ensure it can continue.I think it is important that the research community be heard on this and be heard early.

The American Society for Reproductive Medicine will be issuing a statement on Wednesday supporting stem cell research and opposing attempts to curtail it for political reasons.

I urge you to sign on to the BIO letter, and/or issue your own.

If anyone has any questions, please feel free to get in touch with me.

Sean Tipton
American Society for Reproductive Medicine
stipton@asrm.com
202-863-2494

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Tony Mazzaschi <Tmazzaschi@aamc.org> (Tony Mazzaschi <Tmazzaschi@aamc.org> [UNKNOWN])

CREATION DATE/TIME: 2-DEC-1998 16:39:58.00

SUBJECT: Adhoc: Varmus' Statement on Stem Cell Research

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
For those unable to attend this moning's Senate hearing on stem cell research, a copy of Dr. Varmus' prepared statement follows. The complete hearing was broadcast live on C-SPAN II and is likely to be repeated on either C-SPAN I or II.

Tony Mazzaschi
AAMC

Statement of
HAROLD VARMUS, M. D.
Director
National Institutes of Health

before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies

December 2, 1998

Mr. Chairman and Members of the Subcommittee, I am Harold Varmus, Director of the National Institutes of Health. I am pleased to appear before you to discuss recent published reports on the isolation and propagation of the first human pluripotent stem cell lines. These findings, reported by Drs. John Gearhart from Johns Hopkins University and James Thomson from the University of Wisconsin, bring medical research to the edge of a new frontier that is extraordinarily promising. The development of human pluripotent stem cell lines deserves close scientific examination, further evaluation of the promise of the research, and careful consideration and open discussion of the ethical and legal issues. I want to thank you for the opportunity to discuss this important issue with you and the Members of this Subcommittee.

Why the excitement? For the first time, scientists have obtained human stem cells that can give rise to many types of cells in our body. Let me briefly describe these experiments. Dr. Thomson and coworkers derived stem cell lines from embryos donated by couples undergoing in vitro fertilization
(IVF) as part of treatment for infertility. These cells were grown in culture and found to divide indefinitely and have the ability to form cells of the three major tissue types*endoderm (which goes on to form the lining of the gut), mesoderm (which gives rise to muscle, bone and blood) and

ectoderm (which gives rise to epidermal tissues and the nervous system). The ability of the cells to specialize into the three major tissues types is
an important indicator that these cells are pluripotent. Dr. Gearhart and his coworkers derived pluripotent stem cells from fetal gonadal tissue destined to form germ cells. When grown in culture, these cells resemble other types of pluripotent stem cells in that they, like the cells from Dr. Thomson's work, also can develop into cells of the three major tissue types.

What Are Stem Cells?

As policy makers proceed to consider the scientific, ethical and societal issues raised by this research, it is absolutely essential to clarify terms and definitions. There are many types of stem cells. In general, they all have the ability to divide (and self renew) and to commit to a more specialized function. There is a hierarchy of stem cell types. Some stem cells are more committed than others. Some stems cells - the pluripotent stem cell we are discussing today - have the ability to become many, but not
all, of the cells types in the human body.

Through processes we are only beginning to understand, primitive stem cells can be stimulated to become specialized, so that they are precursors to any one of many different cell types such as muscle cells, skin cells, nerve cells, liver cells. Unlike the stem cells from which they are derived, these specialized cells are "committed" to a particular function.

All stem cells have the capability of self-renewal, i.e., they can continually reproduce themselves. Cells from the very earliest embryo (up to
about the 16 cell stage) are totipotent stem cells. They are "totally potent" or totally capable of forming all cells of the body, including the cells required to support embryonic and fetal development. Each cell of this early embryo has the potential to develop into a human being.

After a few days of development, the early embryo forms a hollow ball of cells, called a blastocyst. This is the next stage of embryonic development.
The clustered cells within this ball are called the inner cell mass. The cells in the inner cell mass are not totipotent. Rather, they are pluripotent. Pluripotent stem cells are more "committed" than totipotent stem cells. Unlike the fertilized egg, or the early embryo, or the intact blastocyst, neither the disaggregated inner cell mass nor the pluripotent stem cells derived from it (nor the pluripotent stem cells derived from fetal germ cells) will produce a human being even if returned to a woman's uterus. These cells do not have the potential to form a human being, because
they do not have the capacity to give rise to the cells of the placenta or other extraembryonic tissues necessary for implantation, nor can they support fetal development in the uterus.

During fetal development, pluripotent stem cells become even more committed, i.e, they have the capacity to form only one or a few different

kinds of cells. For example, hematopoietic stem cells can form all the blood cells, but no other tissue types. The adult human being continues to harbor many types of stem cells responsible for the body's ability to repair some but not all tissues. Stem cells that permit new skin growth and renewal of blood cells are two examples.

Potential Applications of Pluripotent Stem Cells

There are several important reasons why the isolation of human pluripotent stem cells is, indeed, important to science and for the future of public health. At the most fundamental level, pluripotent stem cells could help us to understand the complex events that occur during human development. A primary goal of this work would be the most basic kind of research -- the identification of the factors involved in the cellular decision-making process that determines cell specialization. We know that turning genes on and off is central to this process, but we do not know much about these "decision-making" genes or what turns them on or off. Some of our most serious diseases, like cancer, are due to abnormal cell differentiation and growth. A deeper understanding of normal cell processes will allow us to further delineate the fundamental errors that cause these deadly illnesses.

Human pluripotent stem cell research could also dramatically change the way we develop drugs and test them for safety and efficacy. Rather than evaluating safety and efficacy of a candidate drug in an animal model of a human disease, these drugs could be tested against a human cell line that had been developed to mimic the disease processes. This would not replace whole animal and human testing, but it would streamline the road to discovery. Only the most effective and safest candidate would be likely to graduate to whole animal and then human testing.

Perhaps the most far-reaching potential application of human pluripotent stem cells is the generation of cells and tissue that could be used for transplantation, so-called cell therapies.
Many diseases and disorders result from disruption of cellular function or destruction of tissues of the body. Today, donated organs and tissues are often used to replace the function of ailing or destroyed tissue.
Unfortunately, the number of people suffering from these disorders far outstrips the number of organs available for transplantation. Pluripotent stem cells stimulated to develop into specialized cells offer the possibility of a renewable source of replacement cells and tissue to treat a myriad of diseases, conditions and disabilities including Parkinson's and Alzheimer's disease, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. There is almost no realm of medicine that might not be touched by this innovation. Let me expand on two of these examples.

- Transplant of healthy heart muscle cells could provide new hope for heart attack victims. The hope is to develop heart muscle cells from human

pluripotent stem cells and transplant them into the failing heart muscle in order to augment the function of the heart. Preliminary work in mice and other animals has demonstrated that healthy heart muscle cells transplanted into the heart successfully repopulate the heart tissue and integrate with the host cells. These experiments show that this type of transplantation is feasible.

- In the many individuals who suffer from Type I diabetes, the production of insulin by the pancreas by specialized cells called islet cells is disrupted. There is evidence that transplantation of either the entire pancreas or isolated islet cells could mitigate the need for insulin injections. Islet cell lines derived from human pluripotent stem cells could be used for this critical research and, ultimately, for transplantation.

While I have taken this opportunity to outline the promise of this research, there is much to be done before we can realize these innovations. First, we must do the basic research to understand the cellular events that lead to cell specialization in the human, so that we can direct these pluripotent stem cells to become the type(s) of tissue needed for transplantation in great numbers. And before we can use these cells for transplantation, we must overcome the well-known problem of immune rejection. Because human pluripotent stem cells derived from embryos or fetal tissue would likely be genetically different from the recipient, future research would need to focus on modifying human pluripotent stem cells to minimize tissue incompatibility. Technological challenges remain before these discoveries can be incorporated into clinical practice. These challenges, though significant, are not insurmountable.

How Are Pluripotent Stem Cells Produced?
There are several ways to produce human pluripotent stem cells. These methods have been developed over the past 17 years by researchers working with animals. The work you will hear about today builds on this important basic animal research.

As I mentioned earlier, one method of creating these pluripotent stem cells was described by Dr. Thomson and his coworkers. The techniques they used were initially developed using mice. Dr. Thomson first made stem cells from
non-human primates. In the most recent work, they used inner cell mass cells from blastocyst stage human embryos that were created in the course of
infertility treatment and donated by couples for research to derive stem cells. The researchers allowed cell division to continue in culture to the blastocyst stage and then removed the inner cell mass, which was cultured to
derive pluripotent stem cells.

Pluripotent stem cells can also be derived from fetal tissue, as was first done using primordial germ cells from mouse fetal tissue. Dr. Gearhart and coworkers isolated human primordial germ cells, the cells that will go on to
become eggs and sperm, from 5-9 week old fetal tissue obtained after

pregnancy termination. When grown in culture, these stem cells appear to be
pluripotent.

It may also be possible to make human pluripotent stem cells by using somatic cell nuclear transfer -- the technology that received so much attention with the announcement of the birth of the sheep, Dolly. Although there has been no scientific publication of this to date, presumably any cell from the human body (except the egg or sperm cell) could be fused with an enucleated egg cell and stimulated to return to highly immature, pluripotent and possibly totipotent state.

The Role of the Federal Government

Federal funds were not used in either of the experiments that you will hear about today. First, let me first address Dr. Thomson's work in which cells were derived from embryos created by in vitro fertilization but not used for
infertility treatment. This work falls clearly within the Congressional ban on human embryo research. NIH could not, and did not, support Dr. Thomson's
recent work developing this cell line.

The same restrictions do not apply to Dr. Gearhart's work, although it may be governed by other laws and regulations. Dr. Gearhart derived his pluripotent stem cells from fetal tissue from terminated pregnancies. The Public Health Service Act authorizes Federal funding of human fetal tissue research and provides safeguards for its conduct. The department may conduct or support research on the transplantation of human fetal tissue for
therapeutic purposes if a number of statutory requirements are met. Thus, if Dr. Gearhart's research falls within these boundaries, NIH could have supported his recent work deriving pluripotent stem cells from fetal tissue,
as long as he followed these Federal statutes and regulations. For the record, NIH did not, however, support any of this research.

Ethical Issues

I have just described the science and the medical promise of research on the pluripotent stem cell. But the realization of this promise is also dependent on a full and open examination of the social and ethical implications of this work. The fact that these stem cells were produced from embryos and fetal tissue raises a number of ethical concerns including,
for example, the need to ensure that stem cell research not encourage the creation of embryos or the termination of pregnancies for research purposes.
In strict accordance with the President's 1994 directive, no NIH funds will
be used for the creation of human embryos for research purposes. We also will continue to abide by relevant statutes.

The ethical and social issues associated with stem cell research are

complex and controversial and require thoughtful discourse in public fora to reach resolution. To this end, the President has asked the National Bioethics Advisory Commission to undertake a thorough review of the issues associated with human stem cell research, balancing all ethical and medical considerations.

Summary

The development of cell lines that may produce almost every tissue of the human body is an unprecedented scientific breakthrough. It is not too unrealistic to say that this research has the potential to revolutionize the practice of medicine and improve the quality and length of life.

Mr. Chairman, I am grateful to you for providing a forum to present information about this promising arena of science and medicine. I would be pleased to answer any questions you might have.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME: 9-DEC-1998 10:20:28.00

SUBJECT: Human Genetic Advisory Commission (UK) Report on cloning (includi ng stem cells)

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Everyone has no doubt seen the report of the Japanese cow cloning story today.
In addition, today's Washington Post contains a story about the UK Human Genetics Advisory Commission's latest report "Cloning Issues in Reproductive Medicine and Science (December 1998)" which discusses their views on human stem cell research. The report is available on the HGAC website: www.dti.gov.uk/hgac. I have also ordered hard copies for all Commissioners. We may invite Sir Colin Campbell (HGAC Chair) to our January meeting.

We'll keep you posted.

Eric

Eric M. Meslin, Ph.D
Executive Director
National Bioethics Advisory Commission
6100 Executive Blvd. Suite 5B01
Rockville, Maryland 20892-7508
Tel: (301) 402-4242
Fax: (301) 480-6900
Email: MeslinE@OD.NIH.GOV
http://www.bioethics.gov

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Dr. Lawrence H. Miike" <lhmiike@mail.health.state.hi.us> ("Dr. Lawrence H. Miike" <lhmiike@mail.health.state.hi.us> [UNKNOWN])

CREATION DATE/TIME:11-DEC-1998 16:41:30.00

SUBJECT: capacity report

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
I'm okay, and won't be submitting an individual statement. some minor edits will be sent to eric. look forward to finishing the tissue sample report, and forging ahead with the stem cell report.

larry

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Van Eyck, Laila" <lvaneyck@NASULGC.ORG> ("Van Eyck, Laila" <lvaneyck@NASULGC.ORG> [UNKNOWN])

CREATION DATE/TIME:18-DEC-1998 13:56:29.00

SUBJECT: CGA Conference Call Summary: Dec. 10, 1998

TO: CGA-NEWS@UMDD.UMD.EDU (CGA-NEWS@UMDD.UMD.EDU [UNKNOWN])
READ:UNKNOWN

TEXT:
>CGA Conference Call Summary
>December 10, 1998

>CGA EVENTS:

>The CGA Executive Committee will meet in Tucson, AZ on Jan. 8 and 9,1999 with >dinner hosted by Margie McGonagill, University of Arizona. The meeting of the Committee will take place on Saturday morning. Members will be invited to attend some of the Working Group meetings of the AAU Council on Federal Relations. Katrina >Briscoe has sent detailed information to Executive Committee members.
>
>The CGA Winter Meeting is tentatively planned for March 3-5, 1999 in >Washington D.C. Howard Gobstein, Michigan State University will serve >as chair of the planning committee. The CARET reception on the Hill is >scheduled for March 2. Possible session topics: budget presentations by >agencies; Nethercutt study on NIH; Teacher education; Graduate >education; and EPSCOR.
>
>The CGA Summer Meeting is scheduled for August 8-10, 1999 in Monterey, >California. John Hamilton will serve as chair >of the planning committee.
>
>In 1999, Bob Samors chair of CGA subcommittee >on Research Issues will begin holding monthly conference calls on >research issues.
>
>
>CURRENT ISSUES:

NIH Study in the HOUSE: Bev Lingle reported that Speaker Livingston is not supporting a separate study of the NIH by Congressman Nethercutt. It is not endorsed by Congressman Bliley, chair of the Commerce Committee, either. The reason given was that it was outside the traditional committee structure. The NIH study was designed to replicate the Ehlers study for biomedical research. Nethercutt may continue to conduct a review under the aegis of the Science Committee.

HEA Regulations: The proposed regs on Campus Crime are out now. Others are coming out in bits and snatches. Regional hearings are scheduled

for information purposes. NASULGC will keep CGA members up to date on the latest developments.

>Circular A-110 - April Burke prepared a report in her capacity as Chair of the Regulatory Affairs Committee about proposed changes in management circular A-110. Language was included in the omnibus spending bill >directing OMB to revise Circular A-110 to require federal agencies to >ensure that all data produced under grants are made available pursuant >to Freedom of Information Act. AAU and COGR have sent a letter to OMB >expressing concerns with this provision. Paul Sweet requested that >NASULGC send a similar letter.

>

>HUD Community Outreach Partnership Centers Program - John Hamilton reported that HUD is requesting a >doubling of their grant budget from $7.5 to 15 million. It is seeking >the support of universities. This program may benefit universities that >work with urban communities. This will be raised in the context of the reauthorization of HUD.

>

>Digital Millenium Copyright Act - Cindy Bank reported that universities in their role as on-line >service providers seeking certain exemptions or limitations in Copyright >law must register with the copyright office to designate agents for >notification of claims of infringement. Forms and background information >are located at http://www.lcweb.loc.gov/copyright

>

>Stem Cell Research - Rhonda Norsetter reported that Senator Specter recently held a hearing on the >recent breakthroughs and ethical questions surrounding Stem Cell >Research. In his testimony at the hearing, NIH Director Varmus >recommended that NIH be involved in the study. The House Science >Committee may also look at the use of human embryos in research.

>

>Immigration - If universities are experiencing any problems or concerns >with the implementation of the Immigration Provision in the 1998 Omnibus >Bill, please contact Sang Han at AAU. He is especially interested in >items related to the honorarium issue.

>

>Sallie Mae and Direct Lending - Reportedly, Sallie Mae is contacting >some direct lending institutions and trying to provide them with >incentives to leave the direct lending program.

>

>

>Agriculture Research Funding - Stu Hadley reported that full funding for the authorized Ag research program remains a top priority, and they will be seeking up to $600 million. He suggested CGA members should impress this priority on their Appropriations members.

>RECENT CGA CHANGES AND ADDITIONS:
>Craig Piercy has recently joined Wayne State University and will be the >federal relations representative in their Washington office. The University of Maine has recently opened an office in Washington D.C. >Heather Almquist-Jacobson is the federal relations representative. Both offices are at 499 South Capitol Street, SW, Suite 500B, Washington, DC 20003.

Also, Louisiana State University also has an office in the Washington area. Paul Gravel is the Executive Director. His offices are at 2300 Clarendon Blvd, #300, Arlington, VA 22201. His phone is 703-276-7101.

>
>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Meslin, Eric (OD)" <MeslinE@od.nih.gov> ("Meslin, Eric (OD)" <MeslinE@od.nih.gov> [UNKNOWN])

CREATION DATE/TIME:21-DEC-1998 17:51:21.00

SUBJECT: Capacity update...and dates for 1999

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Commissioners:

We sent the capacity report to the editor for final copy editing. Many thanks to all of you who sent in comments, found typos, suggested edits. I should note that both Jonathan Moreno and Jack Schwartz provided a very helpful read-through.

I need to point out 3 minor changes in the recommendations that were made. I assume you agree with these:

1. Recommendation 1: The word "irregularly" was changed to "occasionally".

2. In Recommendation 2: the title of the panel should be:
Special Standing Panel on research involving persons with mental disorders that may affect decisionmaking capacity.

3. In Recommendation 2 (A), we had intended to repeat the phrase omitted the phrase "that cannot otherwise be approved under the recommendations described in this report" just as it appears in 2(B). Therefore, 2(A) should read:

reviewing individual protocols, that cannot otherwise be approved under the recommendations described in this report, that have been forwarded by IRBs to the SRP for its consideration.

We will try to have the full report available on the web within the next two weeks, and then hard copy will be available a few weeks alter (depending on the printing schedule).

1999 Schedule

Following discussions with Harold, we have decided to schedule further meetings
for 1999 in order to complete the Stem Cell Project.
Some months ago, you received an email from Henrietta which listed the following
1999 dates:

Jan 19-20; (DC)
March 2-3 (DC)
April 17-18 (listed as provisional)
May 11-12 (Madison)
June 29-30 (listed as provisional)
July 13-14 (Cambridge)
Sept 16-17 (DC)

We've decided to try to hold additional meetings in February, April, and June
as follows. Please let me know at your earliest convenience whether you can attend these meetings.

February 2-3 (in Princeton, NJ); 1 1/2 days (First day would start at 1:00pm,
second day would be a full day).

April 15-16, or April 18-19 (in Charlottesville, VA)--as you know, a conference
has been scheduled on April 16-18 at UVA on the Belmont Report. This is not a
commission meeting. However, since all commissioners will be invited to attend
the conference, and many will no doubt be coming--we can try to arrange for a
commission meeting immediately before or after this conference. If the commission meeting occurred on April 15-16, it would be full day 15, half day
16. If it occurred on April 18-19, it would be half day (afternoon), and full
day 19.

June 28-29 (DC)

We intend to finalize the 1999 dates as soon as possible, and to respect the
wishes of the west-coasters who would prefer to have at least one of the DC-area
meetings to be near Dulles airport. Thanks very much for your patience.

Best wishes for the holidays.....

Eric

Eric M. Meslin, Ph.D
Executive Director

National Bioethics Advisory Commission
6100 Executive Blvd. Suite 5B01
Rockville, Maryland 20892-7508
Tel: (301) 402-4242
Fax: (301) 480-6900
Email: MeslinE@OD.NIH.GOV
http://www.bioethics.gov

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Dr. Lawrence H. Miike" <lhmiike@mail.health.state.hi.us> ("Dr. Lawrence H. Miike" <lhmiike@mail.health.state.hi.us> [UNKNOWN])

CREATION DATE/TIME:22-DEC-1998 15:35:19.00

SUBJECT: Re: Capacity update...and dates for 1999

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
I should be able to make the scheduled and proposed meetings.
larry miike

Meslin, Eric (OD) wrote:
>
> Commissioners:
>
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> Eric
>
> Eric M. Meslin, Ph.D
> Executive Director
> National Bioethics Advisory Commission
> 6100 Executive Blvd. Suite 5B01
> Rockville, Maryland 20892-7508
> Tel: (301) 402-4242
> Fax: (301) 480-6900
> Email: MeslinE@OD.NIH.GOV
> http://www.bioethics.gov

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: bkarcher@bio.org (bkarcher@bio.org [UNKNOWN])

CREATION DATE/TIME:12-JAN-1999 11:42:29.00

SUBJECT: Adhoc: Workshop on NIH Grants Stats

TO: stomlinson@bio.org (stomlinson@bio.org [UNKNOWN])
READ:UNKNOWN

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:

Yes, I will attend.

Thanks for the follow-up, I wouldn't want to be left out.

I RSVPed via fax to Micketa Brooks mid last week. It seems there have been breaks in communication over the last two weeks. Two weeks ago my colleagues, Suzanne Tomlinson and Nancy Bradish Myers, RSVPed (via fax) to the AAMC Stem Cell briefing held last week and the faxes never got through.

Please let us know what we can do to prevent this from happening in the future.

Call with any questions. Thanks.

C. Brett Karcher
Government Relations Assistant
Biotechnology Industry Organization

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Alexander Capron <acapron@law.usc.edu> (Alexander Capron <acapron@law.usc.edu> [UNKNOWN])

CREATION DATE/TIME:12-JAN-1999 19:22:01.00

SUBJECT: HESC Topic

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Harold's memo does a nice job of framing the options regarding scope of our project on human embryonic stem cells. He may well be correct that we should raise our sights to encompass #3 (which takes in general "research use of human embryonic and/or fetal material"), but I will wait for the debate on this point at the meeting, as I would hate to see us expend effort on what may be a sure "nullity" before we even begin. Several points from history bear examining, as it is the wise man who learns from experience...and the wiser man who learns from the experience of others.

In that regard, I'll look forward to hearing from the members of the NIH Embryo Research Panel before resolving that issue in my own mind. Moreover, since Harold also includes "fetal material" under #3, I think it would be useful for staff to send
along the recommendations of the earlier (Reagan/Bush era) panel on fetal tissue research and a description (from the media?) of the eventual fate of those recommendations. (I believe Jim Childress was a member of that committee, though my memory may be playing tricks on that question.) My general impression is that both committees, which carved out categories of permissible research, saw their conclusions disregarded, as was also true for the major report of the short-lived Ethics Advisory Board which it recommended that the Secretary of then-DHEW permit federal funding of certain types of in vitro research creating (and then disposing of) fertilized human eggs; in May we will "celebrate" the 20th anniversary of the delivery of that report, which has been gathering dust on the desk of about 7 or 8 subsequent Secretaries of HHS.

I also want to make sure that somewhere in options 1 or 2 is consideration of the issue of embryonic stem cells being capable of being turned into embryos. This is probably at least a three-part question: what is the probability of this happening; if it occurred, is that good or bad; and if bad, do technical means of preventing it exist that wouldn't destroy the utility of the stem cell as a research tool?

See you soon,
Alex

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "r. alta charo" <racharo@facstaff.wisc.edu> ("r. alta charo" <racharo@facstaff.wisc.edu> [UNKNOWN])

CREATION DATE/TIME:12-JAN-1999 20:11:07.00

SUBJECT: alex's query

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
alex wrote:
"I also want to make sure that somewhere in options 1 or 2 is consideration of the issue of embryonic stem cells being capable of being turned into embryos. This is probably at least a three-part question: what is the probability of this happening; if it occurred, is that good or bad; and if bad, do technical means of preventing it exist that wouldn't destroy the utility of the stem cell as a research tool? "

i'd like to urge people to take advantage of jamie thomson's appearance as an opportunity to explore this. as i understand it from conversations with jamie here in wisconsin, stem cells by themselves cannot develop into embryos, only into unorganized masses of cells. the only way to turn a stem cell into an embryo is to do what one would do with any ordinary cell of the body -- use cloning techniques, e.g. nuclear transfer or cell fusion or cytoplasmic injection. but certainly we should confirm that this understanding is correct.

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: National Marfan Foundation <staff@marfan.org> (National Marfan Foundation <staff@marfan.org> [UNKNOWN])

CREATION DATE/TIME:13-JAN-1999 12:23:26.00

SUBJECT: Adhoc: Workshop on NIH Grants Stats

TO: adhoc@aamcinfo.aamc.org (adhoc@aamcinfo.aamc.org [UNKNOWN])
READ:UNKNOWN

TEXT:
>From: bkarcher@bio.org
>Date: Tue, 12 Jan 99 09:47:01 -0500
>To: <adhoc@aamcinfo.aamc.org>, <stomlinson@bio.org>
>Subject: Adhoc: Workshop on NIH Grants Stats
>Content-Description: "cc:Mail Note Part"
>Sender: owner-adhoc@aamcinfo.aamc.org
>Reply-To: bkarcher@bio.org
>
>
> Yes, I will attend.
>
> Thanks for the follow-up, I wouldn't want to be left out.
>
> I RSVPed via fax to Micketa Brooks mid last week. It seems there
have
> been breaks in communication over the last two weeks. Two weeks ago
> my colleagues, Suzanne Tomlinson and Nancy Bradish Myers, RSVPed (via
> fax) to the AAMC Stem Cell briefing held last week and the faxes
never
> got through.
>
> Please let us know what we can do to prevent this from happening in
> the future.
>
> Call with any questions. Thanks.
>
> C. Brett Karcher
> Government Relations Assistant
> Biotechnology Industry Organization
>
>
>
>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Carol Greider <cgreider@jhmi.edu> (Carol Greider <cgreider@jhmi.edu> [UNKNOWN])

CREATION DATE/TIME:13-JAN-1999 08:19:59.00

SUBJECT: ES cells/embryos

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Alta Wrote:
>
>i'd like to urge people to take advantage of jamie thomson's appearance as
>an opportunity to explore this. as i understand it from conversations
with
>jamie here in wisconsin, stem cells by themselves cannot develop into
>embryos, only into unorganized masses of cells. the only way to turn a
>stem cell into an embryo is to do what one would do with any ordinary cell
>of the body -- use cloning techniques, e.g. nuclear transfer or cell
fusion
>or cytoplasmic injection. but certainly we should confirm that this
>understanding is correct.

My understanding is similar to Alta's. Currently in animals, to use ES cells to create an embryo they are injected into a blastocyst (early embryo). This creates a chimeric animal with contributions from both the donor (injected ES cells) and host cell types. Thus there is additional 'embryo research' involved to use ES cells to create an embryo.

Carol

****

Carol W. Greider, Ph.D.
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Department of Molecular Biology and Genetics
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617 Hunterian Building
725 N. Wolfe Street
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phone: (410) 614-6506
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****

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Bernard Lo, M.D." <bernie@itsa.ucsf.edu> ("Bernard Lo, M.D." <bernie@itsa.ucsf.edu> [UNKNOWN])

CREATION DATE/TIME:13-JAN-1999 16:48:53.00

SUBJECT: Additional thoughts on stem-cells and embryos

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
I agree that it would be very useful to get on the record and in the report the types of manipulations required in order to covert stem cells into embryos. We might also want to think about the question of provenance: does it matter that stem cells are derived from the manipulation of and non-implantation of human embryos. This will be the source of the most heated opposition to stem-cell research. Many people accept a gradation: it is more problematic to intentionally create embryos for the purpose of research than to use embryos that would not be implanted in any case. Is there an argument that using already existing stem cell lines is less problematic than creating a stem cell line de novo? This is what might be a new twist on the human embryo research debate. Additionally, what important scientific work could not be addressed by using existing stem cell lines or creating new lines from embryos that were to be discarded. In other words, the policy options are to allow creation of "research embryos," to allow research on embyos that were to be discarded, and to allow research on stem cells that are no longer titpotent and hence do not have the same moral status as embyos. It would be useful to clarify the ethical differences and the scientific implications of using one source of material rather than another.

Bernard Lo, M.D.
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Fax: 415-476-5020

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: alta charo <racharo@facstaff.wisc.edu> (alta charo <racharo@facstaff.wisc.edu> [UNKNOWN])

CREATION DATE/TIME:13-JAN-1999 16:51:54.00

SUBJECT: harold's fax on stem cell project

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
in anticipation of next week's meeting, i'd like to throw out some reactions to harold's memo, which nicely lays out possible project parameters going from the most narrow to the most broad.

harold's first option, to focus only on use of existing stem cells, raises two major areas of analysis:

(a) is work on them morally distinguishable from work on embryos? on this point, the recent emails, emphasizing the biological distinction between embryos and stem cells in terms of their intrinsic potential to develop into babies, seems on point. of course, as the argument from potential has many logical inconsistencies within it, one might conclude that this distinction between stem cells and embryos is unimportant, but then the distinction between embryos and all other somatic cells becomes equally unimportant.

(2) assuming for the sake of argument that work on embryos is morally suspect, is work on the stem cells tainted by their derivation from privately financed embryo research? here there is good literature on the debates surrounding use of data from the nazi experiments in the death camps from which we can develop our own ideas.

thus, there certainly is plenty to talk about on just this topic. nonetheless, it is my understanding that the existing stem cells in jamie's lab cannot supply all the researchers indefinitely with their need for research material, despite the fact that he can replicate the stem cells. this is due to the inherent problem of spontaneous mutations developing when the stem cells reproduce, rendering the supply unusable at some point in time. thus, if we wish to really deal with the question of research just on stem cells, we will have to tackle the question of how one obtains adequate supplies of stem cells on which to work. this, it would seem, means tackling either embryo research or fetal tissue research or both -- i.e., harold's categories (2) and (3). and since there are some questions about the usefulness of stem cells derived from fetal germ cells (jamie explained this to me but i fear i have already forgotten the explanation), it would appear that we would have to tackle embryo research in order to tackle the question of stem cell supplies.

as for (4), i.e. the making of new embryos for research and stem cell collection, i'd suggest that we get a very firm understanding of exactly

how far down the road we can go with stem cell research before we need to get into this. for example, i understand that for stem cells to be used for cell-based transplant therapies, we may well need to have them immunologically matched to the recipient, thus necessitating the use of cloning to generate a de-differentiated somatic cell (otherwise seen as an embryo by many people) that can be developed to the stage where it can become a source of stem cells for auto-transplantation. at the senate hearings, some of the scientists thought this kind of experimental therapy was no more than 5-7 years away for parkinson's disease. if that's the case, one would hope there would be federal policy on this technique sometime in the next three years, so that researchers have time to figure out if they can rely on public funds, will need to seek private funds, or will be faced with state or federal prohibitions that forestall the work altogether.

---

r. alta charo, j.d.
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975 bascom mall
madison, wi 53706

tel: 608-262-5015
fax: 608-262-5485
racharo@facstaff.wisc.edu

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Alexander Capron <acapron@law.usc.edu> (Alexander Capron <acapron@law.usc.edu> [UNKNOWN])

CREATION DATE/TIME:13-JAN-1999 16:21:06.00

SUBJECT: Re: ES cells/embryos

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
On Wed, 13 Jan 1999, Carol Greider wrote:

> Alta Wrote:
> >
> >i'd like to urge people to take advantage of jamie thomson's appearance as
> >an opportunity to explore this. as i understand it from conversations with
> >jamie here in wisconsin, stem cells by themselves cannot develop into
> >embryos, only into unorganized masses of cells. the only way to turn a
> >stem cell into an embryo is to do what one would do with any ordinary cell
> >of the body -- use cloning techniques, e.g. nuclear transfer or cell fusion
> >or cytoplasmic injection. but certainly we should confirm that this
> >understanding is correct.
>
>
> My understanding is similar to Alta's. Currently in animals, to use ES
> cells to create an embryo they are injected into a blastocyst (early
> embryo). This creates a chimeric animal with contributions from both the
> donor (injected ES cells) and host cell types. Thus there is additional
> 'embryo research' involved to use ES cells to create an embryo.

Thanks to you both for the clarification. My question arose both from some of the responses that Thompson et al made to the press at the time of their recent announcements on stem cells and from the comments made when Wilmut first announced Dolly and some scientists speculated that the sheep had been created NOT from a normal somatic cell but either from a fertilized egg or from a stem cell present in the mammary tissue (where, it seemed to be suggested, one would have a greater likelihood of finding a stem cell than in the epithelium). The upshot of those comments seemed to be that performing "cloning" with a nucleus from an embryo or stem cell was less of a "big deal" than with a normal somatic cell---so I was just wondering if that perspective would lead to the conclusion that an embryonic stem cell is really very close to being an embryo (that is easily triggered into becoming an embryo). I understand the answer to be "No; it would still have to be subject to nuclear transfer, etc. and hence is basically not that different than any other cell that can provide a

nucleus for transfer." If this is right, then we should get it discussed on the record and plan to have a clarification on this point in the report, as a way of making clear what issues the development of human embryonic stem cells DOESN'T implicate.

Alex

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "Bernard Lo, M.D." <bernie@itsa.ucsf.edu> ("Bernard Lo, M.D." <bernie@itsa.ucsf.edu> [UNKNOWN])

CREATION DATE/TIME:14-JAN-1999 13:02:59.00

SUBJECT: First reactions to briefing book

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:

After reading the materials in briefing book, I have several observations and suggestions to share.

1. Historically, the debate over embryo research has been dominated by issues of the moral status of the embryo and whether certain answers preclude embryo research, or at least the federal funding of it. I wonder if we can think about how me might broaden the terms of the debate, because if we go down the same tracks, I fear we will reach the same impasse. Perhaps two considerations are pertinent today, which were not salient at the time of the NIH panel deliberations in 1994. First, the prospective therapeutic benefits of stem cell research seem much less speculative today than in 1994. As with the fetal tissue debate, the prospect of important therapeutic benefit may substantially alter the policy discussion. Second, the discussion surrounding non-heart beating cadaver donation for organ transplantation suggests that the public is willing to consider the idea that persons who will not have a long life trajectory, considerations of benefit to others may assume greater moral weight. In some discussions, embryos that are considered to be full persons are given greater respect than live-born persons who are imminently dying on life support and whose relative wish to donate organs. This discrepancy may deserve more attention and analysis.
2. When faced with apparently unprecedented situations, we all tend to draw analogies to other situations. Recognizing the limitations of all such analogies, we might consider the potential transplant donor (for non-heart beating cadaveric donation) as another analogy.
3. When we consider the policy options for providing oversight of research, I would like to learn more about the RAC model for gene therapy. How did it work, from the perspectives of scientists, ethicists, etc. It seems that the scientists thought it was too restrictive/intrusive, whereas some ethicists believed that protocols were approved that didn't give a balanced view of the nature of the prospective benefits. While I personally find a RAC model attractive, it may be one of those good ideas that didn't work out well in practice, at least in its previous configuration.

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Ph: 415-476-5370
Fax: 415-476-5020

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: "r. alta charo" <racharo@facstaff.wisc.edu> ("r. alta charo" <racharo@facstaff.wisc.edu> [UNKNOWN])

CREATION DATE/TIME:14-JAN-1999 20:42:14.00

SUBJECT: bernie's email

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
i agree with bernie that another circuit around traditional arguments focusing on the status of the embryo based on its intrinsic characteristics would be at high risk of simply re-stating the case for an impossible divide in public thinking. the "snark" piece of mine that was included in the briefing book lays out (at somewhat tedious length) my own post-embryo-panel efforts to argue for shifting the debate to different grounds, to wit, an approach i called "political ethics" which sets forth moral arguments about how to balance public interests by supporters and opponents of embryo research, focusing on the distributive justice questions of how the benefits and burdens of the research would be handled. i'd be very interested in others' reactions to the proposals therein, as the piece occasioned little comment after it was published.

At 10:02 1/14/99 -0800, you wrote:
>
> After reading the materials in briefing book, I have several
>observations and suggestions to share.
>1. Historically, the debate over embryo research has been dominated by
>issues of the moral status of the embryo and whether certain answers
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>if we can think about how me might broaden the terms of the debate, because
>if we go down the same tracks, I fear we will reach the same impasse.
>Perhaps two considerations are pertinent today, which were not salient at
>the time of the NIH panel deliberations in 1994. First, the prospective
>therapeutic benefits of stem cell research seem much less speculative today
>than in 1994. As with the fetal tissue debate, the prospect of important
>therapeutic benefit may substantially alter the policy discussion. Second,
>the discussion surrounding non-heart beating cadaver donation for organ
>transplantation suggests that the public is willing to consider the idea
>that persons who will not have a long life trajectory, considerations of
>benefit to others may assume greater moral weight. In some discussions,
>embryos that are considered to be full persons are given greater respect
>than live-born persons who are imminently dying on life support and whose
>relative wish to donate organs. This discrepancy may deserve more
>attention and analysis.

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>draw analogies to other situations. Recognizing the limitations of all
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>How did it work, from the perspectives of scientists, ethicists, etc. It
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>personally find a RAC model attractive, it may be one of those good ideas
>that didn't work out well in practice, at least in its previous
>configuration.
>
>
>Bernard Lo, M.D.
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>521 Parnassus Ave.
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>

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Carol Greider <cgreider@jhmi.edu> (Carol Greider <cgreider@jhmi.edu> [UNKNOWN])

CREATION DATE/TIME:14-JAN-1999 10:04:51.00

SUBJECT: Re: ES cells/embryos

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
Alex Wrote:

> The upshot of those comments seemed
>to be that performing "cloning" with a nucleus from an embryo or stem cell
>was less of a "big deal" than with a normal somatic cell---so I was just
>wondering if that perspective would lead to the conclusion that an
>embryonic stem cell is really very close to being an embryo (that is
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>"No; it would still have to be subject to nuclear transfer, etc. and hence
>is basically not that different than any other cell that can provide a
>nucleus for transfer." If this is right, then we should get it discussed
>on the record and plan to have a clarification on this point in the
>report, as a way of making clear what issues the development of human
>embryonic stem cells DOESN'T implicate.

There are two issues here:

what is a "BIG DEAL" from the scientific stand point of what is going on during "reprogramming of the nucleus" and what is a "BIG DEAL" from the ethical concern standpoint.

We should not confuse these.

>From the scientific standpoint it is less of a 'big deal' to get an early fetal cells to "de differentiate" than is is to get a fully determined adult human cell to "de-differentiate". so scientist might say this is less of a big deal but be talking about something differetn than ethisists.

>From the ethical view point, as you know, some people have a concern about any research that uses any human enbryo or fetal material. Thus for those people it matters not a bit what kind of nucleus is tranfered if the transfer involves a human oocyte and creation of a (possibly?) viable embryo.

Second from the ethical standpoint regarding cloning, as we all know, if people are concerned about "babymaking" it is very different in the public mind to clone from and existing person thatn from an embryo that is not an existing person.

Finally regarding the discussion that others have raised about "already existing ES cells". If you read some of the reviews that came in the breifing book it is apparent that many of the proposed uses of ES cells are to get around immune rejection of tissue transplants. To do this NEW ES cells must be created using nuclear transfer from the person who will receive the transplant. thus limiting the discussion to "already existing ES cells" misses much of the point of proposed the medical benifits.

Carol

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****

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: srctran@world.std.com (Gregory Aharonian) (srctran@world.std.com (Gregory Aharonian) [UNKNOWN])

CREATION DATE/TIME:15-JAN-1999 09:56:18.00

SUBJECT: PATNEWS: Boycott against RiceTec; NIH testifies about techtran/stem cells

TO: patent-news@world.std.com (patent-news@world.std.com [UNKNOWN])
READ:UNKNOWN

TEXT:
!19990115 Boycott against RiceTec; NIH testifies about techtran/stem cells

-- A boycott is being organized against Rice Tec
-- NIH official testifies about technology transfer and stem cells
-- Country study: India - Local species (turmeric, neem and basmati)

Greg Aharonian
Internet Patent News Service

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AUTHOR: Nandita Sharma and Allison Campbell, Basmati Action Group
TITLE: North American Boycott against Rice Tec called
DATE: 29 November 1998
PLACE: Vancouver, Canada
NOTE: Please contact the Basmati Action Group for more information, to indicate your support to their campaign or to share ideas on explanding the campaign to other countries.

BASMATI ACTION GROUP (BAG)
c/o 1957 Kitchener St. Vancouver, B.C. Canada V5L 2W6
Tel. (1-604) 255-4910 E-mail: basmati-action@sfu.ca
Website: http://www.eciad.bc.ca/~lolin/basmati/

NORTH AMERICAN BOYCOTT AGAINST RICE TEC CORPORATION CALLED

November 29, 1998

The Basmati Action Group (BAG) has launched a North American boycott against
the products of Rice Tec Corporation of Alvin, Texas, USA. Rice Tec claims to have invented the basmati rice they sell under the trade name, "Texmati" (Rice Tec products also include "Jasmati" and "Kasmati" rice). The purpose of the boycott is to heighten awareness of the issue of life-patents,

organize public condemnation of this process and demonstrate that the patenting of life will be costly - not profitable - to those that pirate indigenous knowledge and nature's creative capacities. We ask that you support the Basmati Action Group in our boycott of all Rice Tec products.

Why support a boycott on Rice Tec?

Basmati rice has been grown in the Punjab region of India and Pakistan for centuries. Working with nature's own creative capacities, farmers in this area have, over time, cross bred and cultivated this distinct form of rice known for its fragrant aroma and unique taste. For the farmers of India and
Pakistan, basmati rice is a vital subsistence food and source of income.

In 1997, the powerful United States Patent and Trademark Office accepted Rice Tec's application to patent basmati rice (patent # 5,663,484). By cross-breeding two basmati rice varieties, this corporation insists that it has "invented" a "novel" variety of basmati and has patented it as "basmati 867." The Rice Tec patent covers any basmati variety crossed with a semi-dwarf strain grown anywhere in the western hemisphere. Despite Rice Tec's claims of 'novelty', "basmati 867" has been derived from Indian and Pakistani basmati rice lines crossed with semi-dwarf varieties. The basmati varieties used to "invent" Rice Tec's "basmati 867" are farmers' varieties bred over centuries in South Asia. What Rice Tec has done with its patent is to pirate what until now had been communally shared and claimed it as their own private property.

The crux of the issue is not whether the basmati rice variety bred by Rice Tec is "novel" and therefore patentable or not because the facts show that it is not. The real issue is that no one should be able to hold a patent over a life form. By taking out a patent on "basmati 867" Rice Tec is participating in what has been described as "biopiracy."

Biopiracy is the theft of indigenous knowledge, the theft of the creative capacities of nature and the false claim by patent holders - mostly corporations - that they created the life form they have pirated. Biopiracy lays the groundwork for the colonization of creation - of life itself - by scientists and, ultimately, the corporations they work for.

Life-patents further the power of corporations. Imagine a world where nothing is grown except crops that a corporation has claimed 'invention' of and can profit by. Imagine if nothing is grown without farmers having to go to corporations to buy back seeds stolen from them in the first place. Or a world where nothing can even grow without the permission of corporations (i.e. the "Terminator Technology" that prevents plants from reproducing themselves). This is the world that biopirates, and patents like the one on "basmati 867" are already helping to bring about!

We need to fight against this trend. BAG is part of a world-wide movement of
people who are protesting the corporate claims of "invention" that patents on life represent. We are not resigned to living in a world where the creative capacities of nature, of women and of communities of people are systematically denied and pirated. BAG calls for an end to patents on life

forms that is currently being sanctioned by the World Trade Organization and
enshrined in both national and international law.

Victories have been won against corporations that have patented life forms! The US National Institutes of Health "disclaimed" its notorious US patent on
the human cell line of a Hagahai Indigenous person from Papau New Guinea (patent # 5,397,696) after popular outrage was organized. The Indian government revoked the W.R. Grace Corporation's "species patent" on transgenic cotton. In other words, this boycott against Rice Tec can work!

Who is the Basmati Action Group (BAG)?

BAG is a grassroots organization that values life in all its diversity. BAG is opposed to the patenting of any life forms, anywhere, by anyone. This means supporting actions that value and procect ecological integrity, indigenous knowledge and lands, women's rights, the autonomy and self-determinacy of people and community-based action. Food forms the natural link between community and life. For this reason, recent developments in world trade and agricultural policy, life-patenting and genetic engineering strike us as attacks on the essence of those things we value most.

BAG has been formed to raise awareness about biopiracy, life patents and on-going acts of colonialism - and to work to end these practices. Along with many others, we see biopiracy as the "third wave of colonialism" and an entrenchment of sexist and racist practices. We recognize that women in the South ('Third World Women') continue to bear the brunt of acts of colonialism. For over 500 years, the North (the 'First World') has been enriched by stealing from nature and the people's of the South (the 'Third World'). This is maintained by present global economic and political relations. Most of the world's biodiversity is located in the South and biopiracy is an attempt by corporations to privatize and 'own' what is the common heritage of people in the South. BAG is also working to show that biopiracy is a form of class conflict with corporations trying to eliminate communal property, destroy farmers' control and supplant nature's creative capacities in order to increase their own private profits.

How can I support the boycott on Rice Tec?

Please circulate this notice within your organization and to your membership. Talk about biopiracy and the Rice Tec boycott whenever possible.
Spread the word to your contacts across North America. Support local actions
against biopiracy. Ask your local stores to stop carrying Rice Tec products.

Boycotting Rice Tec and its products is one action in the movement to resist
corporate control over life forms. Raising awareness of biopiracy and developing ways of producing and distributing food that are ecologically sound and socially just is something we can all contribute to in different

ways. BAG has also initiated a petition campaign trying to get the Canadian government to refuse Rice Tec's US patent on basmati rice and enacting strong legislation that prevents the patenting of life forms in Canada. This struggle cannot be won without global solidarity - a victory in Canada is impossible without simultaneous victories against the World Trade Organization, NAFTA etc. BAG is working in coalition with people's organizations in both the South and North to revoke Rice Tec's U.S. patent on basmati rice and to stop biopiracy.

Please let us know if we can use your name as a supporter of our campaign in
our future work.

Any suggestions towards strengthening our objectives and resistance is greatly appreciated.

For more information, check out our Web Site.
http://www.eciad.bc.ca/~lolin/basmati/
or call and ask for Nandita Sharma or Allison Campbell at (1-604) 255-4910.
Mailing and e-mail addresses are listed above.

In Struggle,
Nandita Sharma for the
Basmati Action Group

Letter to Stores Carrying Rice Tec Products:

November 29, 1998

NORTH AMERICAN BOYCOTT AGAINST RICE TEC CORPORATION CALLED

The Basmati Action Group (BAG) has launched a North American boycott against
the products of Rice Tec Corporation of Alvin, Texas, USA. Rice Tec claims to have invented the basmati rice they sell under the trade name, "Texmati" (Rice Tec products also include "Jasmati" and "Kasmati" rice). The purpose of the boycott is to heighten awareness of the issue of life-patents, organize public condemnation of this process and demonstrate that the patenting of life will be costly - not profitable - to those that pirate indigenous knowledge and nature's creative capacities. We ask that you support the Basmati Action Group in our boycott of all Rice Tec products.

There are three things you can do to support the boycott on Rice Tec.

1) Remove all Rice Tec products from your shelves immediately, and let us know that you have done so.

2) Stop ordering Rice Tec products. Tell your Rice Tec distributor that you are not willing to support biopiracy in this or any form.

3) Tell your customers that you are boycotting Rice Tec and why.

To facilitate your cooperation, we are holding an information evening on TUESDAY, JANUARY 26, 1999 from 7 to 9 p.m. at Room #4 at the Mount Pleasant
Neighbourhood House (800 E. Broadway - near Fraser St. in Vancouver, B.C.). This meeting will be designed to give store-operators and staff more targeted information so that you may better explain the boycott to your customers. Also at this meeting we will distribute copies of a letter for your customers, explaining biopiracy and the reasons for the Rice Tec boycott.

Please notify us as soon as you decide to support the boycott.

Included in this call for support (sent to those in Canada) is the petition BAG is circulating within Canada. Please photocopy and distribute it. Remember, it is important to return completed petitions to the return address printed on the bottom.

Any suggestions towards strengthening our objectives and resistance is greatly appreciated.

For more information check out our web site.
http://www.eciad.bc.ca/~lolin/basmati/
or call Nandita Sharma or Allison Campbell at (1-604) 255-4910.
Mailing and e-mail addresses are listed above.

In Struggle,
Allison Campbell for the
Basmati Action Group

BASMATI ACTION GROUP (BAG)
c/o 1957 Kitchener St.
Vancouver, B.C. Canada V5L 2W6
Tel. (1-604) 255-4910
E-mail: basmati-action@sfu.ca
Web: http://www.eciad.bc.ca/~lolin/basmati/

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Earlier this week, NIH OTT Director, Maria Freire was one of the panelists called for testimony before the Senate Appropriations Subcommittee on Labor,
Health and Human Services, Education & Related Agencies. As an follow-on of
earlier hearings on the Hopkins/WARF/Geron stem cell projects, the committee
members have become increasing interested in how patent rights & licensing affect basic research product development. For federally-funded technology this means, of course, patenting & licensing practices of universities and Federal labs derived from the Bayh-Dole Act & the Federal Technology Transfer Act.

The NIH testimony on this subject at the hearing (which included a

discussion
of the potential adverse effects of restrictive licensing/MTA practices for research tools) is appended below.

Regards,

Steve Ferguson
NIH Office of Technology Transfer

Statement of Maria C. Freire, Ph.D
Director - Office of Technology Transfer
National Institutes of Health

before the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education and Related Agencies

January 12, 1999

Mr. Chairman and members of the subcommittee, I am Maria Freire, Director of the Office of Technology Transfer at the National Institutes of Health (NIH). I am pleased to appear before you today to address how intellectual property considerations affect basic science and the future development of products for public benefit.

I understand that the subcommittee is particularly interested in how patent rights and commercialization strategies operate in the context of the recent
findings on pluripotent stem cells reported by Drs. John Gearhart from Johns
Hopkins University and James Thomson from the University of Wisconsin. You have previously heard from a panel of experts, including the Director of NIH, Dr. Harold Varmus, on the scientific implications of these findings. Given the complexity of these issues, it is important to understand how the transfer of federally funded technology from the not-for-profit sector -- be it university or Federal laboratory -- to the private sector, is accomplished. To do so, I direct you to the successful process established by Congress in the 1980's that governs the commercialization of federally funded biomedical research.

The Bayh-Dole Act, Stevenson-Wydler Technology Innovation Act of 1980, and amendments, including the Federal Technology Transfer Act of 1986 (FTTA)

Nearly twenty years ago, Congress enacted a series of laws that encourage government owned and government funded research laboratories to pursue the commercialization of the results of their research. These laws are the Bayh-Dole Act of 1980, the Stevenson-Wydler Innovation Act of 1980, including
one of its amendments, the Federal Technology Transfer Act of 1986 (FTTA). The Bayh-Dole Act addresses intellectual property rights in federally

funded
grants, contracts and cooperative agreements, while Stevenson-Wydler and
the
FTTA address intellectual property of government laboratories. The goal of these laws is to promote economic development, enhance U.S. competitiveness and benefit the public by encouraging the commercialization of technologies that might otherwise not be developed into products due to the lack of incentives. Generally, these laws allow government laboratories and the recipients of government funding to elect to retain title to their inventions. They also impose certain obligations: promoting utilization, encouraging commercialization and ensuring public availability of these technologies.

I am pleased to say that these goals have been achieved and expectations havebeen surpassed. Indeed, in the biomedical arena, the impact of these
statutes
has been dramatic. Many experts believe that the biotechnology industry
was
spawned from the close interaction between academia and industry. The Bayh-Dole Act and the FTTA continue to contribute to the global leadership of the U.S. biomedical enterprise. New products developed under this
system
benefit patients daily and provide hundreds of scientists with the tools required for further discovery in support of our public health mission. The NIH intramural program alone has over 150 products on the market, including diagnostic kits, vaccines, therapeutic drugs and dozens of antibodies, cell lines and other research tools. Statistics on the remarkable success of university-based technology transfer activities are also available and I have submitted a recent survey for the record.

To accomplish the transfer of technology, universities have relied on authorities granted to them by the Bayh-Dole Act. The Act permits the
grantee
to retain title to intellectual property developed with federal funds and
to
license its rights to for-profit entities. Patents provide the right to exclude others from making, using, or selling a new invention for the life of the patent. This is society's reward to the owner for teaching others how to make and use the invention claimed in the patent. In the biomedical field, patents are extremely valuable to companies, particularly small companies. They provide a means of securing investment income by establishing the company's preeminence in a particular area of technology. Parties interested in practicing an invention, in which they have no ownership, may obtain rights to the invention by entering into a licensing agreement with the patent owner. A license is a contract with binding commitments on each party, usually involving compensation. A license does not grant title to the invention. Licenses can be exclusive, when only one party is permitted to benefit from the use of the technology, or non-exclusive, when more than one party is allowed to benefit from such rights.

As this subcommittee well knows, new drugs and vaccines are costly to develop;
companies will not invest in further research and development without some

promise of future product exclusivity. When Congress gave federal grantees the ability to patent and exclusively license government-funded inventions, the private sector turned its attention toward publicly supported research as a new source of potential products. The value to the public resides in the generation of new drugs, vaccines, and medical devices. These activities have also stimulated economic development and the creation of new jobs in the United States.

The University of Wisconsin provides us with a good example of how the Bayh-Dole Act is implemented. Early work by Dr. Thomson on non-human primates, such as Rhesus monkeys, was federally funded and therefore, the patent obtained on stem cells arising from this work is governed by this Act. In accordance with the law, the invention was disclosed to the NIH, a patent application was filed by the University, through the Wisconsin Alumni Research Foundation (WARF), and WARF licensed the technology to a small company (Geron). Because federal funds were used for this non-human primate work, the government has a non-exclusive, royalty-free right to use the patented cells by or on behalf of the government. This would allow the government laboratories and contractors the right to use the patented cells for further research. In addition, in handling this invention the University must ensure that the goals of the Bayh-Dole Act -- utilization, commercialization, and public availability -- are implemented.

When research is funded entirely by the private sector, the government has no license, and it is strictly a private matter whether, and under what terms, new intellectual property is made available to others for commercial or research purposes. This is the case for the Geron sponsored work conducted by Dr. Gearhart on human pluripotent stem cells derived from fetuses.

It is usually not the existence of a patent that raises concern for the biomedical research community. The concern arises when the patent holder chooses to exercise its rights through licensing in a manner inconsistent with the advancement of basic research. For example, many new inventions are not final products. The discovery may be a research material or a new method or procedure, primarily useful as the means to conduct further research. Such discoveries are commonly known as research tools. There is little doubt that these research tools may be patentable and that they are of economic value to the holder of these rights. There is also little doubt that the value to society is greatest when such research tools are widely available to scientists.

Mr. Chairman, I cannot emphasize this point strongly enough. Preserving research uses is extremely important to the advancement of science. A license that provides complete exclusivity to a technology that is also a research tool may result in some product development in the short- term, but it will close off opportunities to advance science and develop other products in the long-term. The only way to maximize the benefit to the

public is to ensure that both research use and the potential for commercial development are preserved.

The professionals working in the specialized field of biomedical licensing strive to promote a balance between commercial interests and the public interest. In those instances where a research tool can also become a therapeutic product, licenses can be, and are, carefully crafted by scope, application and field to allow use by the research community without destroying a company's commercial incentive to develop the product. Careful licensing that preserves this balance, however, has not always been the case. The NIH has been concerned for some time about the potential adverse effects of restrictive licensing practices on access to research tools. Dr. Varmus convened a national workgroup to study the issue and make recommendations to the NIH. The report of the workgroup is on the NIH web site:

www.nih.gov./news/researchtools/index.htm,

and NIH expects to publish guidelines for NIH supported investigators this spring, in accordance with the report.

Stem Cell Research

How does this relate to pluripotent stem cells? Pluripotent stem cells provide the research community a springboard to launch numerous inquiries into the most fundamental processes of cellular growth and differentiation that underlie human development. Elucidating these mechanisms provides the foundation for the next generation of biomedical discovery. Such discoveries will be directed toward treatment of human developmental abnormalities, regulation of uncontrolled cellular growth associated with cancer, a source of differentiated cells and tissues for transplantation therapy, and a means to identify new drug targets and test potential therapeutics, among others. Realizing the fullest potential from this new stem cell technology for the American people deserves and requires further inquiry.

Stem cells are a research tool today; hopefully, they will also be developed into therapeutic products in the future. The issuance of patents on these new discoveries by the Patent and Trademark Office may not necessarily have an adverse effect on continuing research, provided that the patent owners devise a licensing strategy that will allow basic research to continue unencumbered while preserving commercial value. We understand that both the Johns Hopkins and Wisconsin licenses to Geron are exclusive at this time, but may allow for the use of these cells by non-profit researchers under certain terms and conditions. These terms and conditions would be set forth in an agreement commonly called a Material Transfer Agreement, or MTA.

MTAs are vehicles used to transfer proprietary materials between and among the for-profit and not-for-profit sectors. While most MTAs are simple, 1 to 2-page agreements, MTAs can sometimes pose problems due to the type of obligations or restrictions imposed by the provider of a material on the recipient. Such obligations can stifle the broad dissemination of

new discoveries, slow the technology transfer process and limit future avenues of research and product development. Examples of such obligations include so-called "reach-through" provisions that may: 1) give the provider
of a material ownership of new inventions developed by the recipient; 2) require royalty payments by the recipient to the provider on inventions discovered by the recipient that are not covered by the provider's patent; or, 3) require options to exclusive rights to any new intellectual property arising from recipient's use of the material. The NIH has minimal authority
with regard to the stem cell patent and patent applications at issue today, and it would be inappropriate for me to try to comment on specific terms and conditions that may be imposed by these parties under the MTAs contemplated.

At NIH, our view is that conditions imposed by patent owners - whether in a license or an MTA - can be crafted to ensure both research uses and commercial development. For example, our strategy is to negotiate non-exclusive licenses whenever possible. This allows more than one company
to develop products using a particular technology, products that may ultimately compete with each other in the marketplace. We recognize that companies need an exclusive market to offset the risk, time, and expense of developing biomedical diagnostic or therapeutic products. However, companies do not necessarily need to achieve that position solely by exclusively licensing a government technology used to develop the product. Instead, companies are frequently able to add their own proprietary technologies to the invention licensed from the government to ultimately achieve some level of uniqueness and exclusivity for the final product.

If non-exclusive licensing does not provide enough incentive for the company
to develop a product, and it often does not for a potential therapeutic application, NIH will award exclusivity for specific indications or fields of use, based on the license applicant's commercial development plans at the
time of the application. NIH also requires exclusive licensees to grant sublicenses to broaden the development possibilities when necessary for the public health. Finally, NIH insists on the continuing unencumbered availability of the licensed technology to not-for-profit scientific community for further research.

Experience over the last 20 years has shown that to maximize public health benefit, the balance between exclusivity and access must be carefully maintained and research uses of new technologies must be preserved. These concepts form the basis for the licensing policies of the NIH, as well as for the proposed guidelines for our grantees mentioned above.

Summary

Congress has enacted legislation for recipients of federal funding that encourages the utilization, commercialization and public availability of federally funded inventions. Grantees have exercised broad discretion and appropriately seek to achieve these goals through the patenting and

licensing
of new inventions that arise through the use of federal funds. If the research is entirely funded by the private sector, the government has no license and is not involved in patenting or licensing decisions. Exclusive licensing, without regard to research uses, can impede rather than enhance utilization and public availability of certain types of inventions, such as research tools. Strategic licensing can alleviate potential problems. Indeed, many grantees provide for the continuing availability of exclusively
licensed subject matter to researchers in order to ensure progress of biomedical research. The NIH has urged, and will continue to urge, patent owners and exclusive licensees to ensure continuing availability under terms that do not limit basic research or encumber future products.

Mr. Chairman, I am grateful to you for providing a forum to present information about the effects of patents and licenses on this promising new area of science and medicine. I would be pleased to answer any questions you may have.

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AUTHOR: Siddartha Pradesh, WTO consultant
TITLE: Country study: India - Local species (turmeric, neem and basmati)
IN: Information Technologies for Development website
DATE: beta version, 1998
URL: http://www.itd.org/issues/india6.htm
NOTE: The Trade and Development Centre is run jointly by the World Trade Organization and the World Bank's Economic Development Institute, under a programme called Information Technologies for Development (ITD). A wide range of sectoral studies, essays, book reviews, links & other research tools is being posted on this website (http://www.itd.org) about development
aspects of the global trade system. Some of the material deals with issues like genebanking and farmers' rights, protecting indigenous biodiversity knowledge, etc. The case study below, meant to counter-argue claims of "bio-piracy", contains many direct links to patents, newspaper articles, NGO websites and other sources.

World Trade Organization & World Bank
Trade and Development Centre

COUNTRY STUDIES: INDIA
PART 6: LOCAL SPECIES - TURMERIC, NEEM AND BASMATI

Some of the biggest controversies on intellectual property rights in India are about patents involving local plant species. Three plants in particular have been the focus of attention: turmeric, neem and basmati rice. In each case, the patents were granted in the United States. But there is some confusion about the exact implications of these cases.

The outcry against patents involving plants that have traditionally been used in India for medicinal or agricultural purposes is based on three broad concerns:

* that farmers will no longer be able to use these products without paying royalties
* that consumers will also be deprived of cheap medicines
* that local communities should receive a share of the commercial gains: after all - the argument goes - the companies owning the patents learnt the value of the species through local knowledge, so they have a debt to repay.

There are also strong counter-arguments. They take the form of a defence of the intellectual property protection (patents, or some other form of protection for plant varieties, for example) in these areas as a means of promoting development through research. They also reject some of the assumptions and conclusions of the criticisms =97 for instance, that patenting means higher costs.

What the cases presented here show is this: whatever you believe about themerits or costs of protecting intellectual property, it is important to
understand exactly what is being protected and whether the protection does or does not have broader implications for the use of the species. There is a lot of confusion and misunderstanding in this area.

One point is clear. By definition, a product or a process that has been used
publicly and traditionally is not new and therefore it cannot be patented. In at least one case, a patent was withdrawn because Indian objectors were able to prove successfully that the idea was not new.

TURMERIC

What is turmeric?

Turmeric (Curcuma longa) is a plant of the ginger family yielding saffron-coloured rhizomes used as a spice for flavouring Indian cooking. Its unique properties also make it an effective ingredient in medicines, cosmetics and as a colour dye. As a medicine, it is traditionally used to heal wounds and rashes.

A turmeric patent

In March 1995, two expatriate Indians at the University of Mississippi Medical Centre, Jackson, (Suman K Das and Hari Har P. Cohly) were granted a US patent (patent number 5,401,504) for turmeric to be used to heal wounds.

The Indian Council for Scientific and Industrial Research (CSIR) filed a case with the US Patent Office challenging the patent on the grounds of "prior art", i.e. existing public knowledge. CSIR said turmeric has been

used for thousands of years for healing wounds and rashes and therefore its use as a medicine was not a new invention.

The claim had to be backed by written documentation claiming traditional wisdom. CSIR went so far as to present an ancient Sanskrit text and a paper published in 1953 in the Journal of the Indian Medical Association. The US Patent Office upheld the objection and cancelled the patent.

Why was the patent withdrawn?

Inventions can only be patented if they satisfy three criteria:

* novelty - only inventions that are genuinely new, and not part of existing knowledge, can be patented.

* non-obviousness - if the new invention is obvious, i.e. anyone familiar with the subject could easily anticipate the invention, then it cannot be patented.

* utility - the invention has to work in practice The turmeric case failed to meet the novelty criteria.

What are the social implications?

In this case, there was no threat to Indian farmers and consumers once the patent was cancelled. This case shows that unjustified patents can be challenged.

Some concern remains, however. The fact that the patent was initially granted shows the difficulty of checking in one country (in this case the United States) whether public knowledge about an idea already exists in another country (in this case India).

Often the check involves a search (by the patent office) for written evidence =97 for example in an existing patent or an academic journal. Searching for existing patents in other countries is becoming easier, even among developing countries, with computerized databases, pooled information,
and international or regional cooperation.

P.S. That's not the only turmeric patent

The US Patent Office database reveals some nine patents using turmeric, the latest for treating degenerative musculoskeletal diseases such as rheumatoid
arthritis and osteoaarthritis.

NEEM

What is neem?

Neem (Azadirachta indica) is a tree from India and other parts of South and Southeast Asia. Growing to 7=AD20 metres tall, it is now also planted in Africa, Central America, the Caribbean and Hawaii. One of the world's largest plantations is in Saudi Arabia, where approximately 50,000 trees have been planted on the Plains of Arafat.

Because of its properties as a natural medicine, pesticide and fertilizer, the neem tree has attracted a considerable amount of international interest.

As a pesticide, neem extracts can be used against over 250 pests including whiteflies, aphids, mealybugs, mites, and termites. It is also effective against fungus diseases such as rusts and powdery mildew that attack the leaves of ornamental plants and food crops.

Its properties are used to cure common colds and flu. The oil extracted from
its seeds can be used to cure various diseases. Mixed in soap, it offers cheap and easy relief from malaria, skin diseases and even meningitis. Neem is grown in semi-arid regions and during droughts, when most crops fail, its leaves provide fodder for livestock.

Neem patents

Numerous neem products have received patents. Several of these have been granted to Indian companies for a range of products including a contraceptive (patent granted to the National Institute of Immunology in 1993) and an environmentally safe pesticide (for Godrej Soaps in 1994).

But the most controversial patents are those granted to the US company WR Grace & Co for extraction and storage processes. They are:

* US patent No 4946681, granted in 1990 for improving the storage stability of neem seed extracts containing azadirachtin (a substance obtained from Azadirachta (neem). (The inventor is named as James F Walter of Ashton, Maryland.)

* US patent No 5124349, 1994 for storage of stable insecticidal composition comprising neem seed extract. The major contribution was increasing the shelf-life stability of azadirachtin solution. (Four people are named as the inventors.)

The WR Grace patents provoked a national outcry. Under pressure from these groups, the Indian government filed a complaint to the US Patent Office accusing WR Grace of copying an Indian invention. However, in the end, the government withdrew its complaint as it realized that the US-based company had in fact created a new invention for the neem extraction process, and the patent was not based on traditional knowledge.

Are the fears valid?

The neem patents aroused a number of complaints. Farmers protested that the patents would prevent them from using neem as a source of home-made pesticide. Non-government organizations used the incident to challenge European and US patents on the grounds of =93bio-piracy=94. A coalition of 200 non-governmental organizations from 40 countries have challenged the patents, fearing they would put pest control costs out of reach for farmers who are now using the extracts in underdeveloped nations.

In fact, the patents granted to WR Grace & Co are quite specific.

The 1990 patent is for a method of producing neem extract that can be stored
well. The abstract says: 'Storage stable pesticide compositions comprising neem seed extracts which contain azadirachtin as the active pesticidal ingredient wherein the compositions are characterized by their non-degrading
solvent systems. In a first embodiment, the pesticide compositions contain solvent systems characterized as having greater than 50% by volume aprotic solvents and less than 15% by volume water. In a second embodiment, the pesticide compositions contain solvent systems characterized as having greater than 50% by volume alcohol and less than 5% by volume water. The pesticide compositions contain surfactant concentrations of at least about 1.0%, up to 10%.'

The 1994 patent is for a specific method of extracting and treating active substances from neem seeds so that the resulting solution is stable enough to store. The abstract says the patent is for a =93process for the production
of stable azadirachtin solutions comprising extracting ground neem seeds with a solvent having azadirachtin solubility to produce an aqueous-containing azadirachtin extract solution and then adding an effective amount of 3=AD4 Angstrom molecular sieves to selectively remove water from the extract to yield a storage-stable azadirachtin solution having less than 5% water by volume=94.

It is only these specific newly invented processes that are covered by the patents. Farmers always have and will continue to be free to use neem in any traditional way they desire.

The use of neem extract, or its seeds or leaves, cannot be patented, since they have been used for centuries. Its properties can only be patented if they are considerably modified. For instance, any synthetic variation of a naturally occurring product is patentable, as it does not occur in nature in that form.

BASMATI

What is basmati?

Basmati is a top-quality rice from the Punjab provinces of India and Pakistan. The word means 'fragrant earth', and the rice is a slender aromatic long grain variety that originated in this region and is a major export crop for both countries.

What is protected?

There are two distinct issues here, involving three aspects of intellectual property rights.

1. The patent. In September 1997, the US Patent Office granted a patent to US firm RiceTec Inc (patent number 5,663,484) covering 'novel' varieties of basmati rice, their plants and seeds, a method of breeding them and a method
for selecting rice grains (by examining their starch content) so that the cooked rice has the same qualities as traditional basmati.

It is important to be clear that the patent does not (and cannot) cover the use of the name 'basmati' or any other name. It simply deals with the varieties and various methods of dealing with them. Fears that the patent would give RiceTec exclusive right to use the word 'basmati' in the United States are therefore entirely incorrect.

2. The name. Various reports have referred to the US company's use of such names as 'basmati', 'Kasmati', 'Texmati' and 'Jasmati'. See for example an item in Scientific American magazine.

In fact, the company has used the brand names Kasmati, Texmati and Jasmati in the United States and United Kingdom since before the patent was issued. It has been using the term 'basmati' as a generic term for considerably longer: 'RiceTec has produced and marketed Texas basmati and American basmati rice - and labelling it as such - for 20 years and exporting the products for 15 years with no objection ever previously raised', a company statement says.

In other words, the name and the patent are completely separate issues; and there is also a distinct difference between the use of basmati as a generic term, and the use of brand names such as Texmati and Jasmati.

('Jasmati' is a combination of 'basmati' and 'jasmine' - the latter term originally used to describe a Thai variety of fragrant rice that is quite different from 'basmati'.)

Two types of intellectual property are involved with the names: trademarks and geographical indications (the use of place names or words associated with a place to identify the origin, type and quality of a product - for example 'champagne'). Since the word 'basmati' is not a place name, its validity as a geographical indication would depend on whether 'basmati' can be shown to be closely and exclusively associated with a geographical area.

The debate

1. The criticisms
Three broad complaints have been raised by critics of the RiceTec patent and the separate issue of the use of names such as Texmati and Jasmati.:

* that the collective intellectual and biodiversity heritage of Indian and Pakistani farmers is being 'stolen'

* that the patent and/or trademark allow(s) the US company to 'steal' the markets of Indian traders and exporters by describing US-grown rice as 'basmati'

* that consumers are being misled because the word basmati is being used for
an American-grown rice which is derived from Indian rice but not grown in India, and hence not of the same quality.

2. The patent
The Indian government has protested that the patent could affect annual basmati exports worth $277m and thus threaten the livelihood of thousands of
Punjabi farmers. But so far it has not formally challenged the patent, and therefore the question of whether a significantly novel step has been taken to justify the patent remains unchallenged in law.

Critics also claim that US law allows patents to be issued for inventions made in the US even if the same inventions have been made in other countries
- but this is untrue as the turmeric case shows.

3. The name
First the generic term 'basmati'. Critics in India and Pakistan say the term
should not be used for rice grown outside the Punjab region. But for many years 'basmati' has been grown elsewhere, and not only in the United States.
In Thailand, a company called Siamati has been trying for several years to produce basmati commercially. Basmati is also grown in Uruguay.
Under international agreements such as the WTO's intellectual property pact,
a name associated with a geographical region can be used elsewhere if the name has become generic. For this reason =93cheddar=94 cheese is produced all over the world, and not just in the part of the United Kingdom identified by the name.

For basmati, the debate about whether it is geographic or generic continues.

For the American industry, the position is clear. On 9 July 1998 the USA Rice Federation declared that 'the terms basmati and jasmine refer to types or generic classes of aromatic rice and that these terms cover many varieties and a broad range of qualities. Additionally, these terms are

not restricted to products or varieties produced in any specific country or groups of countries.'

RiceTec also observes that Indian researchers have used the term 'basmati' to describe fragrant rice from countries other than India and Pakistan.

But that view is questioned in India.

Second, the trademarks. RiceTec's trademarks registered in the United States
have not been legally challenged although some critics have suggested that the names could mislead consumers.
RiceTec has applied for trademark registration in the United Kingdom. In February 1998, the Indian Agricultural and Processed Foods Development Authority (APEDA) said it would oppose RiceTec=92s trademark application for basmati in the United Kingdom.

APEDA says the UK has established a Code of Practice for rice which allows the term basmati to be used only for the long grain aromatic rice grown in India and Pakistan. Therefore, APEDA believes that the case is winnable in favour of India, but the case remains unsettled.

RiceTec says that despite the opposition, there have been no lawsuits or other legal actions in the UK. 'The fact is that RiceTec has not sold any product in the United Kingdom due to the European Union import levy which discriminates against US specialty rice products in favour of India and Pakistan', RiceTec says.

4. Theft and deception?
As to the accusations of 'theft' and deception, RiceTec says it 'invented a way to produce basmati rice in the United States comparable to the best basmati grown in India and Pakistan and we received a patent to protect our breeding method and seeds. Those countries do not have such laws and, thus, few people there understand what they [the patents] do and don't do.'

RiceTec denies that it took germplasm (the genetic material) from India or Pakistan or that it used biotechnology or genetic transformation to producethe patented new basmati lines. The germplasm 'came partly from the World
Collection of Germplasm in Aberdeen, Idaho, which is operated by the Agricultural Research Service of the US Department of Agriculture', RiceTec says, adding that it used 'traditional, classical' breeding techniques over a period of 10 years.

RiceTec says its production of high quality products and the new breeding methods it has developed 'help feed a hungry world and reduce land requirements'.

AND FINALLY, BIO-PIRACY?

The questions of whether local communities have a right to a share of intellectual property royalties, or even whether substances found in nature

should be patentable, is complicated.

It partly depends on one's judgement of whether a particular invention represents a big enough leap into new knowledge - knowledge that is far removed from local or traditional wisdom. It also depends on views of how best to deal with biodiversity.

These issues are being discussed in a number of international forums, including the WTO's Committee on Trade and Environment.

Some countries have reached agreement with commercial firms, allowing the companies to undertake research into local species on condition that payment
is made to the host country or that there is some technology transfer to allow local scientists to take over the research later.

Opinion is also likely to continue to differ on whether intellectual property protection such as patents help or hinder a community's ability to discover new medicines or agricultural materials. Similarly, for the question of the best way to handle biodiversity.

But while the issue continues to rage in India, it is notable that the Indian government has come some way towards endorsing the view that intellectual property protection is beneficial - in areas where Indians are strong, such as computer software, movie-making and some areas of design, the government is keen to enforce protection.

Written and researched by Siddhartha Prakash, WTO Consultant
Edited by WTO Information and Media Relations Division

RECORD TYPE: FEDERAL (NOTES MAIL)

CREATOR: Alex Capron <acapron@law.usc.edu> (Alex Capron <acapron@law.usc.edu> [UNKNOWN])

CREATION DATE/TIME:15-JAN-1999 14:01:26.00

SUBJECT: Re: First reactions to briefing book

TO: NBAC Members E-list <nbac-members@lists.Princeton.EDU> (NBAC Members E-list <nbac-members@lists.Princeton.EDU> [UNKNOWN])
READ:UNKNOWN

TEXT:
In reply to Bernie's suggestions/queries:
1. I urge us to stay away frm the nonheartbeating cadaver analogy. It is itself an enormously controversial area. I for one believe that the usual protocol for using such donors violates the letter and spirit of the determination of death statutes and would be rejected by many people if they understood that. Trying to construct a tortured analogy from there to embryos (i.e. if we're willing to terminate life of person with little prospect of long life so that he/she can be used as organ donor shouldn't we be willing to terminate life of embryo so he/she can be used as stem cell donor?) is not only problematic in itself but runs the risk of importing an additional controversy. I hope we can keep it off the table.

2. In my view, the RAC worked well in both scientific and ethical terms for many years; the problem arose (in HArold Varmus' view) when companies that were not, strictly, required to seek RAC review (because no federal $) sought it anyway (which had a virtuous implication) rather than only going with FDA; as I understood Varmus' view, a lot of the science involved wasn't very good and it was not only a waste of RAC time to review it but was really being used by the companies to hype their "cutting edge" new "therapies" (which was useful in venture capital terms, compared to the behind-closed-doors FDA review). From the viewpoint of those of us on the RAC, there was also the sense that a lot of what we were doing was repetitive and that kept us from looking at the truly unresolved issues, such a transfers that might lead to germ-line changes. LeRoy Walters has written about the RAC and could be asked to come talk about it.

Alex