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The Human Tissue Trade

Issue: Human tissue - including genes, cells and their components - is the building block of human life and a critical area for investigation and treatment of diseases and genetic factors that threaten our lives. The analysis and study of human genetic variation - between individuals and populations - is critical to the resolution of current and future health problems and is now a major focus of medical research worldwide. Despite the promise of medical breakthroughs, the utilization of human tissue prompts intense ethical concerns regarding ownership of human biomaterials, eugenics, discrimination, and medical confidentiality. A large and growing South to North and North to North movement of human tissue is now taking place in an almost total policy and regulatory vacuum. International tissue exchange routes, open to and including corporate and military participation, are developing without respect for patient confidentiality and prior informed consent regarding commercialization, patenting, and in some cases, tissue reproduction and exchange. This global trade in parts of the human body has outstripped efforts to ensure tissues are collected and used responsibly.

Market: Currently a US \$428 million a year industry, the market for tissue culture products and processes is predicted to grow at an average of 13.5% per year and may be worth nearly US \$1 billion by 2002.¹ Industry proponents predict a US \$80 billion annual value of human tissue culture products within a generation. Every major pharmaceutical transnational - supported by universities, human genome sequencing, computer software and hardware companies, and blood and tissue banks (including the Red Cross) - is active in the field.

Policy Implications: The UN High Commissioner for Human Rights, the International Court of Justice, and the UN General Assembly should all play a role in addressing these issues. In addition, the World Health Organisation and professional bodies such as the World Medical Association must be involved. Before taking action, governments must consult the rural populations, indigenous peoples, and health-targeted groups such as the disabled whose tissues are in highest demand and who bear the greatest risk in the human tissue trade.

Introduction

The culture and study of human tissues with genomic technologies promises major medical breakthroughs; but also presents profound, unaddressed international policy and ethical concerns. The global trade in human tissue - especially that of rural populations and indigenous peoples - has expanded dramatically in recent years and has far outstripped efforts to create policy mechanisms to ensure the rights of tissue donors. The tissue trade is the foundation of a burgeoning industry that depends on patenting and selling pieces of the human body and gathering and providing access to proprietary genomic information.

This Communique investigates and analyzes current global collection and trade patterns for human tissue. In particular, it highlights the example of the International Histocompatibility Workshop (IHW), one among many projects - with varying levels of organisation and implementation - that are collecting human tissues that may be immortalized, characterized, and, in some cases, patented and sold.

Few, if any, people and organisations have a handle on the ethical and legal implications of the rapidly expanding tissue traffic. This gap in international

policy must be quickly addressed by appropriate multilateral bodies and professional organisations if patients' and research subjects' rights are to be enforced.

Humanity in a Bottle: The Tissue Culture Industry

Tissue culture is the reproduction of microorganism, plant, and animal cells in the laboratory. The culture of human cells is crucial for the biotechnology industry. When kept under proper conditions, "immortalized" human cell lines can reproduce in perpetuity and provide an infinite quantity of cells that contain the unique DNA of the original tissue donor. Valuable human tissues also include simple frozen tissue samples (usually blood) which, when preserved correctly, retain DNA and proteins which can be stored, tested, and sequenced, and whose properties can be recorded in computer databases and called up (or thawed out) in the future.

Using gene sequencing equipment and electronic communications, scientists can even create a set of instructions for producing unique bits of DNA found in a given tissue sample, send those instructions around the world, and have a colleague synthesize the DNA of interest in a remote location.

But these new technologies have not supplanted the need for human tissues to be physically interchanged. In fact, such technologies and the intellectual property systems that permit the monopolization of human tissue combine to form a powerful industry whose existence depends on the exchange and sale of human tissue, tissue products, and equipment for growing it.

Either through their own efforts, or through alliances with other biotechnology companies, major pharmaceutical multinationals are moving to secure a place in the tissue culture industry.

Selling Cells

The Market for Human Tissue and its Products

According to the US consulting firm Frost and Sullivan, the worldwide market for cell lines and tissue cultures brought in US \$427.6 million in corporate revenues in 1996. Frost and Sullivan predicts that the market will grow at an average annual rate of 13.5% over the next 7 years and by 2002 be worth US \$914.1 million.²

Products derived from cultured tissues are worth considerably more. For example, Genentech, a US company which is majority owned by Switzerland's Roche, uses cell culture to make "Activase", a blood clot-dissolving drug administered to persons who have recently suffered heart attacks. Activase is made by a hamster ovary cell line modified with human DNA that has been spliced into the hamster cells from a human melanoma cell line. Activase rakes in US \$200 million in sales per year.³

Blood cells from the umbilical cords of newborn infants, which have potential therapeutic applications later in life, are now stored - for a fee - by several companies. Meanwhile in Europe and the US, health authorities, patent offices, doctors, activists, and companies fight over who should profit from this business and how.⁴

One internet directory of tissue culture-related enterprises currently lists 38 companies in the US alone which specialize in selling cells, cell products, and tools for cell culture. Some have internet home pages where customers can peruse on-line catalogues of "normal" and/or "mutant" human tissue for sale.⁵

According to Frost and Sullivan, the human tissue industry has a marketing problem. Its companies have a hard time differentiating their cell lines from those sold by other companies. As a Frost and Sullivan press release puts it "The users of cell culture products view them as commodity items for which there is no difference between vendors and products." Frost and Sullivan says that industry is moving to emphasize product differentiation in order to bolster human tissue prices. It seems likely that companies will seek even more patent protection for their human tissue products and processes in an effort to set themselves apart and monopolize pieces of the growing market.

The Future of Tissue Culture? ⁶

Using the core technology of human cell culture, scientists are now rapidly developing the field of tissue engineering. By culturing cells on three dimensional growth grids (or "matrices"), they hope to be able to grow replacement human organs (or pieces of organs) in the near future. Scientists are currently working with human skin, muscles, cartilage, heart valves, and artery, blood, liver and kidney cells for transplant applications.

"What we're doing is holding a Pandora's Box, which is the cell."

-- Dr. Peter Johnson, Director of PTEI

The city of Pittsburgh (US) is trying to become a centre of the new field, which its proponents say will be a "\$80 billion dollar a year manufacturing industry" when it matures. Together with local universities, the city has formed the Pittsburgh Tissue Engineering Initiative Inc. (PTEI) which aims "to promote regional economic development through the advancement and commercialization of tissue engineering and related technologies." In addition to attracting industry, PTEI offers advice on patenting to tissue engineering scientists and help to universities who want to sell academic researchers' work to industry.

Dr. Peter Johnson, a plastic surgeon who heads PTEI, envisions a future where tissue engineering products will be routinely implanted into people whose own organs are diseased, have been lost, or do not function. New organs will not merely take the place of old ones, but might improve on them through genetic enhancements. Johnson cites the possibility of regulating "skin hue" through genetically-engineered replacement skin, and says "the sky is the limit when it comes to the role of gene therapy with tissue engineering."

Frequent Fliers

The Global Traffic in Human Tissue

An unfortunate reality currently confronts the enormous number of people who, for clinical or research purposes, give blood or other samples of their tissue. They may unwittingly become a statistic in the international human tissue trade - in some cases even if the tissue donor simply gave blood for a blood bank. Donors' cells may be frozen and/or immortalized and shipped across town, across the world, or both. Genetic profile information from analysis of the cells - directly, partly, or unrelated to the purposes for which they were collected - may be created and placed in a database available to thousands.

For instance, whole blood samples given by persons with unusual blood characteristics who register to be bone marrow or platelet donors at a Red Cross centre in rural Japan are distributed internationally for research purposes. Recipients include the University of California at Los Angeles (US) and the Canadian Red Cross.⁸ The ultimate disposition of these samples at their international destinations - whether they were immortalized, used and discarded, stored, or further distributed - is unclear.

In many places, especially in the North, human tissue is banked. Well-known human tissue collections

include those at the US American Type Culture Collection (ATCC) and the European Collection of Animal Cell Cultures (ECACC) in Porton Down, UK. Other, less well-known collections exist that have thousands of blood samples and cells lines from people across the globe and with varying levels of documentation of their origin.

In the United States, for example, more than 250,000 sex offenders and other criminals have been sampled. The US military expects to have collected and stored more than 3 million blood samples of its own troops by 2001. Several US states have saved collections of over 1 million blood spot cards (called Guthrie Cards) collected from newborns.⁹

In Colombia, the Genetics Institute of the Universidad Javeriana in Bogotá, has an enormous collection of tissue samples from Colombian indigenous people. It sent 2,305 blood samples to the US National Institutes of Health laboratory which "invented" the Hagahai cell line that was patented by the US Government.

The Coriell Institute, a US non-profit research organisation and tissue bank, distributes cell lines from diverse peoples and places, including: Karitiana and Surui (Brazil), Biaka (Central African Republic), Huaorani (Ecuador), Mayan (Mexico), Maori (New Zealand/ Aotearoa), Quechua (Peru), Bougainville (Papua New Guinea), Pima, Pueblo, and Cheyenne (all US), and Mbuti (Zaire). A researcher who is just interested in DNA (as opposed to cell lines) can order the "Human Diversity Collection DNA Pool", which consists of "Pooled DNA sample consisting of equal quantities of DNA from 13 males and 15 females from the following populations: Mayan Indian, Karitiana Indian, Suri Indian, Quechua Indian, Auca Indian, Jemez Pueblo Indian, Cheyenne Indian, Khmer Cambodian, Southern Chinese, Japanese, Druze Arab, Nasioi Melanesian, Biaka Pygmy, and Mbuti Pygmy. Two individuals from each of the populations were selected for the pool. Researchers who receive Coriell cells must pledge to not share them with third parties or patent them.

But it isn't always the case that such pledges are requested by tissue banks distributing large quantities of human tissues. The Human Biological Data Interchange (HBDI), a US government-funded tissue bank for diabetes research in Pennsylvania (US), advertises "availability, for immediate distribution... cell lines and DNA from 385 families with diabetic and unaffected siblings." The cells lines include "pedigrees" (multiple cell lines from various members of a family) from US, Swedish, Italian, and Dutch people as well as "Bedouin Israeli", and possibly Colombian indigenous people. The number of cell lines banked per family varies widely, from just 2 or 3 up to 86. In some cases, HBDI offers to contract with interested researchers for the custom collection of additional samples. HBDI makes no effort to restrict patenting of cell lines in the collection (or products of the cell lines). Instead, HBDI sidesteps the issue, saying "HBDI has made no attempt to determine outstanding rights on the cell cultures or other matter in the HBDI repository. HBDI disclaims any

knowledge relating to property interest in the human biomaterials provided", and goes on to refer potential patent seekers to the source family of cell lines.¹⁰

Possibly the most extensive organized effort currently underway collecting, characterizing, and distributing human tissue is the International Histocompatibility Workshop (IHW), a loosely-organized group of scientists of different specialties who focus their study on a region of the human genome known as the Major Histocompatibility Complex (see page 4). For its twelfth meeting, which took place in France in June, 1996, the IHW gathered information on over 26,000 human tissue samples collected by participating laboratories. 366 of these samples were immortalized into cell lines and distributed as a group (called a "cell panel") at the meeting in France.

A summary of the "ethnic origin" of human cell lines distributed in the workshop panel is on page 5. The summary uses the same descriptive terms used in the IHW data.

The IHW's cell panel manager is the ECACC, which invited IHW participants to order the entire panel, or just parts of it. The cell lines are now part of the ECACC's permanent collection and, like those from the cell panels of previous workshops, can be ordered by interested laboratories.

Although the terms under which the ECACC distributes these cells are somewhat more restrictive than those used by HBDI, the ECACC does not prohibit researchers from patenting or otherwise commercializing the IHW cell lines. Instead, it requests that any researcher who "wishes to exploit or use any of the cell line(s) or any progeny or derivatives thereof on a commercial basis... make a formal written request to the ECACC". The ECACC then checks with the lab that deposited the cells - which, importantly, might or might not be the sample collector - to see if commercialization is OK.¹¹

Scavenger Hunt: Where do Samples Come From?

Where do the tens of thousands of samples in the human tissue trade come from and for what purposes are they collected? Samples are rarely, if ever, collected for the specific primary purpose of immortalization and distribution. More often, they are collected through a variety of means including surgery, volunteer participants in disease research, and transplant/transfusion tissue donations. They can also be collected from cadavers. In many cases, research subjects and/or patients may be aware and approve of the reproduction and use(s) of their cells; but in thousands of cases they may not. For instance:

- Colombian indigenous peoples' cells sent to US government and corporate researchers were collected as part of human genetic diversity research program by academic researchers. These researchers were operating with grants from the public sector and industry (including pharmaceutical multinationals). Colombian indigenous peoples' leaders say

About Histocompatibility, Tissue Typing, and Human Genetic Diversity

Histocompatibility specialists study the diversity of the Major Histocompatibility Complex (MHC), a group of many genes tightly clustered together on chromosome 6. One of the most studied and most diverse areas of the human genome, genes located in the MHC produce a number of proteins called human leukocyte antigens (HLA) that are crucial components of the immune system. Histocompatibility's primary medical application is in human organ and tissue transplantation.

For people who need organ or tissue transplants (e.g. bone marrow or certain blood products), the tissue they receive will ideally produce exactly the same set of HLA that their body naturally produces. If there is an HLA mismatch in transplanted tissue, a patient's body is far less likely to accept the transplant. Intricate knowledge of the HLA system also helps doctors develop and utilize immunosuppressive drugs which overcome HLA differences and make more matches between organ donors and recipients possible. HLA types for persons of European ancestry are currently much better understood than those of other people. Consequently, even assuming equal access to medical care, persons of non-European ancestry are disadvantaged in terms of doctors' understanding of their immune system and availability of transplant tissues.

The process of detecting and identifying HLA is called tissue typing. Additional applications for tissue typing have been found in disease diagnosis (some antigens are linked to diseases like juvenile diabetes) and in the courts, where HLA can be useful in paternity testing. Tissue typing requires only a few milliliters of whole blood or cultured cells from a cell line. To date, over 100 HLA have been identified and work continues to identify more.

HLA is highly polymorphic (variable) between individuals; but because HLA is inherited in a person's genes, particular HLA and/or combinations of HLA can be associated with different population groups. For this reason, tissue typing is also of interest to researchers who study the migration and origin of different human populations. By tissue typing enough individuals from populations of interest and testing for the frequency of a particular antigen (or gene) or combination of antigens (or genes), scientists can attempt to trace the history of a given population by examining its degree of relationship with other people.

The field of tissue typing is currently undergoing a major transformation. In the past, scientists used serological methods to type tissue by exposing samples to various antisera which react to specific HLA. Starting in the 1980s and expanding more recently, scientists have begun to identify new antigens and type tissue through the use of DNA amplification and direct DNA sequencing. Rather than detecting the proteins produced by the MHC, scientists - especially those in the North, where expensive DNA sequencing technology is more common lab equipment - are now going straight to the source: the genes themselves.

About the International Histocompatibility Workshop

HLA diversity was first recognized in the 1950s¹² and the importance of tissue typing in organ transplantation was identified in the mid-1960s.¹³ Scientists working in different parts of the world began to identify antigens and, prior to DNA-based methods, develop the serological tests necessary to detect them. Since these tests were dependent on rare, hard-to-develop antisera, histocompatibility experts established a loosely organized international system to exchange the testing materials they had developed.

Known as the International Histocompatibility Workshop (IHW), this informal international exchange system has met periodically (twelve times to date) in different locations for scientists to exchange methods, information, and materials. IHW's leadership consists of committees and coordinators drawn from workshop attendees. Human tissue samples shared at the IHW meetings are gathered from laboratories in advance and assembled into a "cell panel" that consists of hundreds of individual cell lines. IHW participants can order their own copy of the entire cell panel, or portions of it.

In November 1993, two months after the organisational meeting of the Human Genome Diversity Project (HGDP) in Sardinia, the IHW established an Anthropology Component, a subsection of the workshop that is dedicated to studying HLA diversity in populations worldwide.

Information regarding the location and method of sample collection is not provided in all cases. This is due to various reasons, including: the submitting laboratory did not perform the tissue collection, the tissue collection is proposed and has not yet taken place, or for unknown reasons the submitting scientists chose not to provide collection details.

Those entries that do document collection details most often list blood banks and hospitals as the source:

No Information Provided/Unknown	59
Blood Banks	40
Hospitals	18
Research Control Groups	10
Obstetrical Care	2

The database includes comments and descriptive fields filled out by submitting laboratories that sometimes reveal considerable detail about the samples being collected.

Many populations in the database are from remote rural areas worldwide. Examples of database entries include the following notes: One Mexican indigenous people being sampled "communicates through radio messages"; a population of Iranians "do animal husbandry and cultivation", and "95% [of a Chinese population] are peasants". A German lab was particularly descriptive, noting that one Amazonian indigenous people it had obtained samples of "subsist by simple agriculture, hunting and gathering" and that a population from Papua New Guinea "live in villages, e.g. village Tauwema: 300 people."

Many populations in the database were originally collected for non-IHW purposes, including samples originating from legal disputes and women receiving obstetrical care. A population from Kuwait is described as having been in part collected from women having "recurrent spontaneous abortion", while a French lab is working with Algerian samples from "random healthy pregnant women undergoing [a] legal prenatal checkup". A South African lab submitted a population to the study that was collected from "parents in paternity disputes". An Australian Aborigine people was sampled "via renal workup".

The wildly varying kinds of anthropological details submitted suggest collecting samples and genetic information was a considerably higher priority for the IHWAC than learning anything else about study populations. In cases in Spain (involving persons born in Guinea Bissau) and the UK, labs submitted populations and noted they were looking for an anthropologist or a "local contact" with knowledge of the sampled people after collecting tissue from them.

In Europe especially, many labs were interested in confirming peoples' family background with an emphasis on populations being "genuine" (one lab says "both parents genuine Inuits"). An Italian lab looked for samples in part based on surnames, "three generations residence in the area", and "closeness of archaeological sites". Spanish researchers confirmed that a population only included persons with "three past generations being of Spanish origin."

The Anthropology Component Database

Following IHWAC's France workshop, on August 3, University of Geneva Anthropologist Alicia Sanchez-Mazas (or one of her coworkers) placed a copy of a database on IHWAC cell lines in a public directory of one of her department's internet-connected computers. Five days later (August 8), an internet cataloging "robot" called Altavista found the database and indexed its contents. A month later, while using Altavista in internet research related to US Government patent applications on the cells of indigenous people, RAFI found the database in Geneva after typing in search keywords that matched phrases found in the database.

The database was clearly not intended for public consumption and was likely made available temporarily for scientists to share information. Sanchez-Mazas or her coworkers then forgot about the copy of the database in the public file or were not aware that its contents might be indexed by a robot. Consequently, it was left available to anyone with a modem and internet connection.

The database is named "ihwc", probably an abbreviation of "International Histocompatibility Workshop Cells", while the data set containing all the information in the database is called "newpop", short for "new populations". The type and format of the data strongly suggests that the database's entries are an electronic version of information sheets filled out by scientists who submitted details about study populations during the St. Malo conference. Anthropology Component documents available on the internet refer to "registered populations" and it is likely that the database is population registry information provided by laboratories submitting (or planning to submit) the cell line(s). Sanchez-Mazas, Patricia Dard (another University of Geneva anthropologist) and others, were apparently in the process of adding comments, correcting, and editing this information to create a consistent data set on the diverse group of populations.

Other kinds of descriptions are inconsistent and/or unexplained. Mental health factors are not mentioned in the database except in the case of a single group of Austrians described as "parents of schizophrenics". A group of Indians were considered "very fair in colour and sharp features", while for other Indian populations no mention of physical appearance is included. A group of Mexicans was partially described as "middle and low socio-economic cultural class". Several Chinese populations were described by a Japanese lab in terms of their ancestors, including one which "dominated China during the Yuan Dynasty."

Despite the near-universal disavowal of race as a valid scientific concept, laboratories often noted "inbreeding" in study populations and provided racial descriptions of study groups. One Indian population was described as "an important example of historical racial admixture", while a Russian group was said to "belong to the large Caucasian race... the weak Mongoloid mixture is noticed."

IHW's International Transfers of Human Tissue

The map on page 8, which is based upon the IHW cell panel list and the Geneva database, illustrates a

small portion of the international exchange of human tissues through the IHW. It does not show:

- materials not transferred through third countries as part of the cell panel collection process
- the distribution of tissues through the cell panel, which is an ongoing process managed by ECACC.
- direct tissue exchanges between individual laboratories, which may be more numerous than those made for the cell panel.

Thus, despite the broad international exchanges depicted, the map represents only a small portion of the actual transfer of human cells in this single project.

Leaky Pipes

Confidentiality and Data Security Lapses

The confidentiality of personal medical information is critical in any circumstances where research is being conducted or care provided. In the context of international biomedical research, maintenance of confidentiality is complicated by new technologies that facilitate the rapid international transfer of research data, including patient histories and genetic information specific to individuals.

Laboratories' rapidly expanding capability to create or recreate human biomaterials on the basis of electronically-transmitted sequence information presents a further challenge. While this capability is currently limited to relatively small genes and gene segments, this may not be the case for long. In the information age, confidentiality systems that could previously be enforced by simple mechanisms like a lock and key have become an anachronism for labs in much of the world.

Major confidential portions of the IHW's database on over 26,000 human cells - over 11,000 of which are part of the Anthropology Component - were compromised.

Public confidence in biomedical research is and will continue to be directly linked to laboratories' fulfillment of their commitments to confidentiality, no matter what technologies and collaborations are employed in the course of research.

The 12th IHW's management of such information plainly demonstrates severe shortfalls in the protection of research subjects. IHW researchers left detailed patient information on public data servers at the IHW central data collection and analysis centre in Toulouse (France). For a period of at least eight months, anyone in the world with access to the internet could obtain thousands of IHW records containing confidential medical information.¹⁹ Major confidential portions of the IHW's database on over 26,000 human cells (over 11,500 of which are part of the Anthropology Component) were compromised.²⁰

The data sets are sufficiently detailed so as to identify individual persons who donated tissues and, in at least one case, even includes patients' names. The data sets include information on several IHWAC populations

and groups from other IHW studies. Examples include:

- Full name, medical history, and HLA profile of juvenile arthritis patients of a participating US lab.
- HLA profiles, medical information, sex, date, and place of birth for rural Russian persons whose cells are included in the IHWAC study. Similar information was also included on persons born in Guinea Bissau.

Prior to publishing this Communique, RAFI contacted the IHW and requested removal of this confidential medical material from public areas of the internet.

Cashing In Patents and Profits

For some laboratories, research interest in human genetic diversity isn't just about science and the advancement of knowledge, it's also about patents and profits. Thousands of human genes are claimed in pending patent applications. In many cases, the research leading to these gene patents heavily depends upon diverse human tissue samples that the patenting researchers pick up from the global human tissue market.

For instance, potentially highly-profitable US patents and patent applications on genes linked to Alzheimer's disease, asthma, and diabetes have depended upon tissue samples from rural populations and indigenous people.²¹ The US government has patented the cells of an indigenous person (and later abandoned the claim), and tried to patent two more indigenous peoples' cell lines. In none of these cases is it likely that the donors of the material that contributed to the patent will see any of the financial or medical benefits that their tissue donations have made possible.

The blurred lines between medical research and commercial interests extend to laboratories participating in the IHWAC. Several IHWAC participants have filed for and received patents on human cells, cell products, and other HLA-related processes or techniques. For example: James McCluskey, an IHWAC participant who works at Flinders Medical Center in Australia has an 84 country patent (WO 95/12814) on human cell lines used in diagnostic tests for autoimmune diseases. McCluskey is working with Australian Aboriginal peoples' cell lines in the IHW.²² John Hansen, a US cancer researcher and coordinator of the next IHW, has patented cancer therapy methods that include claims on antigens and hybridomas containing human biomaterials (US 5,273,738). Another participant has patented an HLA screening procedure to identify persons susceptible to an unusual blood disorder sometimes affecting patients taking the antidepressant clozapine (US 5,223,399).

Making money from the use of human tissue is not strictly limited to the culture of tissue itself. Bioinformatics uses computer technologies to aid clinical and industrial use of genetic information.

Bioinformatics companies develop new computer systems capable of rapid sequencing and characterization of DNA and information retrieval and analysis systems that collect and provide information from public and private databases. It is a burgeoning technology on which gene boutique companies (see RAFI Communique May/June 1994) depend when sequencing genes.

One of the newest bioinformatics companies is Genomica Corporation, a US company founded in 1996 with investments from two venture capital firms. The founder of Genomica is Dr. Thomas Marr, who also holds posts at Cold Spring Harbor Laboratory (a US non-profit research center heavily funded by the US government) and the US National Cancer Institute. Marr specializes in developing software to access and analyze genetic information held in databases. Marr is also the chair of the informatics committee of the Human Genome Diversity Project (HGDP).²³

Genomica is trying to distinguish itself from other bioinformatics startup companies through a "high-powered" scientific advisory board of geneticists and bioinformatics specialists. The board includes Dr. Aravinda Chakravarti, a well-known US geneticist and member of the panel of the National Academy of Sciences (NAS) which is advising the US government on funding for the Human Genome Diversity Project (HGDP).²⁴

It is unclear if Marr intends to put knowledge gained through the HGDP into Genomica or if the NAS or US government will consider Chakravarti's dual roles a potential conflict of interest.

Genetic Weapons New Light on the Dark Side

International concerns about the potential application of genetics research to weapons production were underscored late last year when the World Medical Association (WMA) spoke out about this possible abuse of genetic knowledge. At the WMA's 48th General Assembly in October in South Africa, the WMA adopted a statement on weapons proposed by the British Medical Association (BMA). The statement focuses on the possible development of genetic weapons, saying:²⁵

"The potential for scientific and medical knowledge to contribute to the development of new weapons systems, targeted against specific individuals, specific populations, or against body systems, is considerable. This could include the development of weapons designed to target anatomical or physiological systems, including vision, or which use knowledge of human genetic similarities and differences to target weapons."

Last year, RAFI investigated policy controls in the United States that regulate the transfer of human tissue samples between civilian and military researchers and discovered that there are none. This means that current and past collections made by civilian researchers worldwide may be used by US military

researchers (See RAFI Communique March/April 1996).

But as the WMA speaks up and US military researchers are obtaining human tissue samples from citizens of South American, Pacific, and possibly African countries, some advocates of human genetic diversity research are insistent that there is nothing to worry about. HGDP spokesman Henry Greely points to the HGDP "Frequently Asked Questions" ("FAQ") document on the internet when the question of potential military use of samples arises. The HGDP contradicts the WMA's opinion, stating:²⁶

"Genocidal use of genetics is not possible with any currently known technology. On the basis of what we know of human genetic variation, it seems impossible that it will ever be developed."

Just a few weeks after the WMA conference in South Africa, US technology writer Ed Regis published an article in the technophilic magazine *Wired* that reports the US military is taking the possibility of a future world of genetic weapons very seriously.

Regis says he was an invited participant in a US Army conference, organised by the wargames division of defence contractor Science Applications International Corp. (SAIC), where invitees discussed military biotechnology possibilities including how "Enemy leaders, for example, [might] be knocked off by means of genetically engineered super-pathogens that are so selective in their behavior they're capable of targeting specific individuals..." and how biological weapons "could selectively wipe out crops and livestock, and could do it with plausible deniability."²⁷

That SAIC would be organizing such a discussion is no surprise. The company is active in developing military and bioinformatics technologies, principally under US government contracts, often with US government foreign intelligence agencies. At Fort Detrick (near Washington), SAIC manages human (and plant) tissue collections of the US National Cancer Institute and US Army biowarfare defense units. SAIC also has a collaborative agreement with InCyte, a gene sequencing company with thousands of patent applications on human tissues, to develop new high-speed gene sequencing equipment (see RAFI Communique May/Jun 1994 and Mar/Apr 1996).

The Human Tissue Policy Vacuum

As of 1995, there were 148 commercial or academic human tissue depositories in the United States alone.²⁸ Canada has at least 75 facilities. How secure are these banks? A survey of Canadian facilities found that fewer than a third of workers handling human tissue samples were aware of any institutional policies related to the management and distribution of samples, although most felt such policies were necessary. Although 61% of the responding staff shared sampled with other parties, less than half sought the consent of the original, donor before doing so. One third of those surveyed were prepared to

make samples available for research beyond the original purpose of the sample. The survey authors concluded the "ethical integrity" of Canadian human genome research was endangered.⁴⁰

European scientists are taking the lead in collecting global human genetic diversity; but, alarmingly, there is no specific legislation related to human tissue anywhere in the European Union.

Although human tissue sampling is assumed to be as extensive in Europe as North America, comparable data is not available. European scientists are taking the lead in collecting global human genetic diversity;

but, alarmingly, there is, no specific legislation related to human tissue anywhere in the European Union. While tissue and data banks in London, Toulouse, Porton Down, Athens, Leiden, Geneva, Turin, and other European cities add to their data and cell line collections, countries like Germany, Switzerland, and The Netherlands do not even have legislation related to organ transplants.⁴¹ It is among these European banks, too, that the greatest ethical blunders in confidentiality have been found. As the EU considers new biotechnology and intellectual property rules, governments and parliamentarians might first consider if they have their house in order as far as medical ethics and the trade in human tissue is concerned.

Human Genome Diversity Pandemonium: What is the IHWAC's Relationship to the HGDP?

It seems that nobody quite has a handle on the IHWAC's relationship to the Human Genome Diversity Project (HGDP). Two of the IHWAC's key researchers are members of the HGDP International Executive Committee. So is the husband of one of these researchers. Four other IHWAC participants also attended HGDP's organisational meeting in 1993, including the manager of the IHW cell panel.

RAFI referred to public HGDP and IHW documents and press reports, and asked participants for clarification of the ambiguous relationship. After considerable hesitation and confusion on the part of many people who RAFI contacted, the answer that seems to have emerged is that IHWAC and HGDP are separate - for the time being. Here, in chronological order, is what we found out:

September 1993: Report from HGDP's organisational meeting in Sardinia (Italy).²⁹

"The HGD Executive Committee will have as its first priorities... the implementation of the pilot project"

1994 Annual Report of Julia Bodmer's lab (UK, member of the HGDP international executive committee).³⁰

"As a contribution to both the 12th International Histocompatibility Workshop Anthropology study and the Human Genome Diversity Project we have collected 160 samples from individuals indigenous to the Orkney Islands."

June 1995: Julia Bodmer in a newsletter for IHW participants:

"At least 81 of the registered populations [in the IHWAC] are to be offered to the Human Genome Diversity Project"

1995 Annual Report of Julia Bodmer's lab:³¹

"The anthropology study will be used as a pilot study for the Human Genome Diversity Project."

October 1996: Quoted in a US science magazine, Henry Greely (principal HGDP spokesperson in the US):³²

"no collecting is going on anywhere in the world under the auspices of the HGDP, although there are projects in Europe and China that may have started collecting and that may eventually become part of the HGDP".

January 1997: Edmund Yunis (IHW participant in the US):³³

"My understanding is that [a formal relationship between IHW and HGDP] will be proposed at the next workshop."³⁴

William Klitz (key IHW participant in the US):³⁵

Declined to confirm or deny any relationship between the IHW and HGDP. Klitz has submitted 3 populations of Mexican indigenous people to the IHWAC.

Henry Greely:³⁶

"none of us knows anything about [Bodmer's 1995 report]... I will let you know what I find out about it."

Alicia Sanchez-Mazas (key IHW participant in Switzerland, attended HGDP's first organisational meeting):³⁷

"[My lab] is comparing populations to reconstruct historical relationships... the work is independent of the HGDP."

Bryan Bolton (ECACC Tissue Bank, attended HGDP's first organisational meeting):³⁸

"Yes we are playing a role in the HGDP but so far I am not aware if any of the existing cell lines have been identified. I am waiting to hear from Dr. Julia Bodmer."

Julia Bodmer:³⁹

"The Pilot Project of the HGDP referred to, in the future tense, in our 1995 report does not yet exist. It was to be, and may yet be, as intended, a pilot study using a very small subset of samples from around the world... No samples have been collected for, or turned over to the HGDP for any such pilot project by or through the International Histocompatibility Workshops."

Growing Problem Requires Global Action

The human tissue trade is not an issue that is going to get smaller. Failure to put the appropriate policies and regulations in place will result in damage to Human Rights and medical research. Civil Society (especially indigenous peoples and health-targeted groups such as disabled people) and government must address the policy questions now while they are potentially manageable. Action can be taken in several fora.

World Health Organisation: Rights to - and research on - human tissues crosses a number of inter-governmental jurisdictions but is the focus of none. Issues surrounding medical confidentiality and medical ethics (including prior informed consent) concern the World Health Organisation (WHO) and non-governmental bodies such as the World Medical Association (WMA). These health organisations have unfinished business. Ultimately, there must be a legally-binding protocol covering prior informed consent to commercialize, patent, or even immortalize or export human tissue. Currently, the rules regarding benefit-sharing in medical research prohibit financial rewards for subjects of medical research while allowing researchers to seek patents, royalties, and other profits arising from the same research. The solution is not to pay the poor for their body parts but to permit community-wide control and benefit-sharing where the tissue involved is shared by a family or community.

It is difficult to understand how medical organisations can sanction research in human tissue in the absence of internationally-acceptable and enforceable protocols - or even sustained efforts to achieve these protocols. There is evidence of abuse. This report clearly shows the lack of protocols is allowing unethical practices.

UNESCO: The general issue of the collection and study of biodiversity has been discussed by the UNESCO Bioethics Committee. Wisely, the Committee has refused to endorse the Human Genome Diversity Project although it has determined to monitor its activities. In RAFI's opinion, the HGDP has been systematically proven incapable of managing its self-appointed mandate. It is time for UNESCO to take on the issue of human biodiversity in all its cultural, scientific, and ethical dimensions.

HGDP: At its outset, the HGDP concluded that the likelihood of commercial interest in human biodiversity was negligible. We now know that the human tissue market could reach US \$80 billion within a generation and that half of all new medical research could be genome-based within a few of years.⁴²

The HGDP similarly concluded that the possibility of intellectual property on human tissues was extremely remote. Within months of this conclusion, the US Government had applied for three patents on the cell lines of indigenous people. Now there are hundreds of patents granted on human biomaterials and thousands more patent applications pending.

The HGDP continues to argue that it is not possible to target specific populations for biological warfare. Yet the British Medical Association and the World Medical Association see this as a serious threat and the US Department of Defense has even simulated scenarios using such weapons.

The HGDP has been unable to keep abreast of the social, commercial, and scientific applications of human genome research. The HGDP has been unable to even coordinate itself. Thus we have the confusion and embarrassment surrounding the HGDP's pilot project and its uncertain connection with the IHW Anthropology Component.

It is also clear that the IHW - including its many members who are also active in the HGDP - has not come to grips with the management of the movement of human tissue and associated data. There are severe and unacceptable problems of confidentiality and prior informed consent that have not been addressed.

For the sake of human well-being, medical researchers need to be able to collect, document, and study human diversity. This work must be done under the direction of the people (indigenous people, rural communities, disabled people, etc...) who are major subjects of the research through a United Nations agency. The HGDP is incapable of this work.

UN Human Rights Committee: The issues addressed in this report are fundamentally those of Human Rights. The UN Committee on Human Rights should be asked to review the various Conventions and protocols that touch on the ownership and control of human biomaterials in order to determine if new technologies require updates to these agreements. In particular, the opinion of the Human Rights Commissioner may be necessary in determining the revision of work on this issue for various UN agencies.

UN General Assembly: The issue of the patentability and Human Rights associated with human tissues must be discussed by the UN General Assembly. UNGA will convene a special session to review Agenda 21 in June 1997. An outstanding concern is the place of human biodiversity within the framework of the Biodiversity Convention. Although most countries concur that human diversity should not be managed by the 1992 Convention, legal interpretation of the Convention suggests that human biodiversity is part of the agreement. In order to correct this problem and assign responsibility more appropriately, the General Assembly may seek an Advisory Opinion from the International Court of Justice (ICJ). The ICJ could be asked to determine the position of humans within the Biodiversity Convention and whether or not patenting of human tissue, as required by the World Trade Organisation (WTO) contravenes Human Rights. If the Court follows the normal practice of providing an Opinion within a year, it will come in time for the Fiftieth Anniversary of the Universal Declaration of

Human Rights in 1998 - and before the review of the WTO's patent provisions in 1999.

- 1 "USA: Cell Cultures are Increasingly Important to Manufacturing in the Biotechnology Industry"; Businesswire, 28 May 1996.
- 2 Businesswire, 28 May 1996
- 3 Businesswire, 28 May 1996 and http://www.gene.com/Medicines/activase_insert.html.
- 4 Biocyte, a US corporation holds a US and European patent on all therapeutic uses of umbilical cord blood cells. The patent has been challenged in both places. If the patent is allowed to stand, persons who benefit from transplants of their own (or others) umbilical cord cells may have to pay royalties to Biocyte in order to do so.
- 5 <http://www.pittsburgh-tissue.net/brochure/Marketplace/UScompanies.html>. See <http://www.clonetics.com/catalog.htm> for an example of an on-line human tissue catalog. Clonetics catalogs their human cell lines as "part numbers". A European example of on-line human cell sales can be found at <http://www.cytotech.dk>.
- 6 See <http://www.pittsburgh-tissue.net> for extensive information about PTEI.
- 7 Internet users can hear a December 1996 interview with Dr. Johnson at: <http://www.annonline.com/interviews/961202/>
- 8 Personal communication with Dr. Satoshi Saito, Nagano Red Cross Blood Center (Japan), 1 February 1997.
- 9 McEwen, Jean M., "DNA Sampling and Banking: Practices and Procedures in the United States", paper presented at the First International Conference on DNA Sampling, Montreal, Quebec, September, 1996.
10. "Human Biological Data Interchange: A Catalog of Family Pedigrees, Cell Lines and DNA for Research", Philadelphia (US), n.d., late 1996 version.
- 11 ECACC's Material Transfer Agreement and 12th Workshop Order Form, available from the ECACC.
- 12 <http://www.aabb.org/docs/sscc-1.html>
- 13 <http://www.umds.ac.uk/elsewhere/tissue/what1.html>
- 14 Source: XII IHW Cell Panel List, available from the ECACC.
- 15 XII IHW Cell Panel List, available from the ECACC.
- 16 At time of publication of this report, the database can be found in Microsoft Access and plain text format by anonymous ftp at <ftp://anthropologie.unige.ch/pub/projects/IHWC/>. If the database is removed from this location, a copy will be made available at RAFI's WWW site at <http://www.rafi.ca>.
- 17 In some cases multiple related populations were listed together in database entries, making a precise definition of the number of populations listed somewhat arbitrary. 130 is a minimum total of the number of populations included in the database.
18. Personal communication with Dr. Julia Bodmer, January 1997.
- 19 The primary internet ftp (file transfer protocol) site used by IHW researchers is located at the Centre Interuniversitaire de Calcul in Toulouse, France at <ftp://ftp.cict.fr>. The username and password to access medical records at this location was provided multiple world wide web editions of the IHW's newsletter "Express" at <http://web.cict.fr:8200/12ihwc/>. RAFI has contacted IHW and requested removal of the confidential materials from these and other public internet locations used by IHW researchers.
- 20 Figures on the IHW database size are as of June 1996 as reported by IHW at <http://www-sv.cict.fr/12ihwc/news/c/dca.htm>
- 21 See RAFI Communique, March/April 1996 and May/June 1995.
- 22 WO Patent #95/12814, "Transfected cell lines expressing autoantigens and their use in immunoassays for the detection of autoimmune disease" and
- 23 "USA: Leaders in Genetics, Bioinformatics Join Genomica SAB; Company Forms High-Powered Scientific Advisory Board", PR Newswire, 17 September 1996.
- 24 PR Newswire, 17 September 1996.
- 25 "World Medical Association Statement on Weapons and Their Relation to Life and Health", statement adopted by the 48th WMA General Assembly, Somerset West, South Africa, October 1996
- 26 <http://www-leland.stanford.edu/group/morrinst/HGDP-FAQ.html>
- 27 Regis, Ed "BioWar" in Wired, November 1996, pp. 146 and 153
- 28 McEwen, Jean M., "DNA Sampling and Banking: Practices and Procedures in the United States", paper presented at the First International Conference on DNA Sampling, Montreal, Quebec, September, 1996.
- 29 <http://www-leland.stanford.edu/group/morrinst/Alghero.html>
- 30 http://www.icnet.uk/lis/ipub/scirep/lif/005_pub.html
- 31 <http://www.icnet.uk/lis/ipub/scirep95/004.html>
- 32 Quoted in The Scientist, 14 October 1996.
- 33 Telephone interview with RAFI, January 1997.
- 34 John Hansen, a US cancer researcher from Washington State who is coordinating the next IHW, did not return messages requesting information about the next workshop.
- 35 Telephone interview with RAFI, January 1997.

- 36 Personal communication, January 1997
- 37 Telephone interview with RAFI, January 1997.
- 38 Personal communication, January 1997.
- 39 Personal Communication, January 1997.
- 40 Verhoef, M.J. et al, "Ethical Issues in Current Human DNA Banking Practices in Canada", paper presented at the First International Conference on DNA Sampling, Montreal, Quebec, September, 1996.
- 41 Quintana, Octavi. "Human Tissue Banks in Europe", paper presented at the First International Conference on DNA Sampling, Montreal, Quebec, September, 1996.
- 42 Alexander Pope quoted in McKusick, Victor, Keynote Address for the First International Conference on DNA Sampling, Montreal, Quebec, September, 1996.