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Phase II for Human Genome Research – Human Genetic Diversity Enters the Commercial Mainstream

Issue: The first major phase of the vast global scientific campaign to map the human genome is nearing completion. With computer-assisted DNA sequencing machines running faster and more cheaply than its originators ever imagined, researchers are now turning from the crude "generic" map of the Human Genome Project (HGP) to its inevitable Phase II – the drive to plunder, patent, and privatize the commercially-important bits of variation found in individuals, indigenous peoples, disease and disability groups, and ethnically-distinct communities. Taking advantage of a U.S. Patent Office decision that makes possible the patenting of minute genetic variations (known as SNPs or "snips"), biopharmaceutical companies are gearing up to redirect the tools they perfected in Phase I to gather up human genetic diversity in Phase II.

Profits: The real money in human diversity mapping lies in single nucleotide polymorphisms (SNPs) that code for specific traits including diseases. The Gene Giants are hoping to patent SNPs in order to develop diagnostic kits, monitoring instruments, and even "designer" drugs tagged to the specific DNA of wealthy customers. Hundreds of millions of dollars are being spent in the effort to find and control SNPs but the long-term profits will be in the billions and could ultimately restructure the entire health care industry.

Players: All of the Gene Giants (the Life Industry's pharmaceutical majors) are actively involved. Human genomics (gene-sequencing) enterprises – the "SNP Caesars" - are also in hot pursuit of human diversity. Other "bit" players include many prominent academic and research institutions and such consortia as the ill-defined (and fated) Human Genome Diversity Project (HGDP). Not least involved are the millions of people with distinct genetic characteristics of commercial interest.

Policies: When RAFI undertook its study of the Human Tissue Trade two years ago, we concluded that the collection and management of human diversity was taking place in an "almost total policy and regulatory vacuum." Since then, the Human Rights abuse of research subjects has worsened and governments and intergovernmental institutions have fallen all over themselves trying to sidestep responsibility for this complex ethical and medical conundrum. At the international level, action must be expected from the UN Human Rights Commission, from the World Health Organization, and from UNESCO's International Bioethics Committee (which has woefully neglected the intellectual property and commercial issues arising from human DNA collection).[1] Nationally, governments could review their medical ethics and research protocols to guarantee the rights and dignity of their citizens. In particular, governments might consider legislation that would *criminalize* the collection or removal of human germplasm without the prior informed consent of the individual, their community, and the national government.

Introduction

Phase I of the great global scientific venture to map the human genome is sprinting to completion years ahead of its original schedule. Late in 1999, the Human Genome Project's leadership predicted that they would complete the identification and sorting of the estimated 3.5 billion genetic "letters" in human DNA by the end of 2000 – perhaps three years ahead of schedule. That this accomplishment is something more than biotech bravado was emphasized by a second announcement, this time by a powerful and respected private enterprise known as Celera that it had jumped far beyond its own previously disclosed identification of a billion "letters" to 2.7 billion – almost three-quarters of our genetic make-up. The race was on to see who would dominate the human genome – the publicly funded HGP or the privately backed companies like Celera[2]. Were the commercial value of human genetic diversity research ever in doubt, those

misgivings were unambiguously laid to rest when Iceland sold its genetic heritage to the genomics company deCODE, who, in turn, hawked the human data to Hoffman LaRoche of Switzerland for US $200 million. The spectacular and controversial deal turned genomics research overnight from an obscure biotech niche industry into a mainstream commercial venture. Suddenly, almost unheard of genomics companies like Millennium (US), Genset (France), and Axys (US), are patenting diversity studies into a multi-billion-dollar commercial product strategy aided and abetted by researchers at universities and even some governments. The extension of patentability by the US Patent and Trademark Office to single nucleotide polymorphisms (SNPs- the smallest unit of genetic variability) has further galvanized commercial pharmaceutical enthusiasm for the new industry. SNPs are the genetic basis upon which diversity researchers define their investigations and distinguish individuals and human populations from one another.

Given this full-scale commercial foray into diversity research in combination with the new methods of sampling and sequencing, the pressing question for ethnically unique populations and particularly for indigenous peoples is no longer "Will we be sampled?" but rather "Who will have access to human genetic diversity, and will it be subject to exclusive monopoly control?"

This issue of *RAFI Communiqué* focuses on the issues surrounding human genetic diversity research. For instance, serious concerns have been raised by the expansion of patentability to SNPs and by the numerous corporate initiatives to privatize human genetic diversity, especially through large-scale sequencing programs and proprietary databases. The current status of the Human Genome Diversity Project (HGDP), the problem-plagued global initiative to collect and sequence human genetic diversity, is discussed; so is its commercial value. The *Communiqué* concludes with recommendations for future action.

Human Genetic Diversity Studies Hit the Scientific Mainstream

"*What are SNPs, and how can you use them? …The Human Genome Project's just the warm-up. For, precisely put, there isn't really a 'human genome' - there are about 6 billion of them."*

> Bruce Goldman, in *Signals*, "the online magazine of biotechnology analysis for the biotechnology industry," August 1999.

The Biological Background

All of the genetic variation in humans (and other species) is the result of small differences in DNA (deoxyribonucleic acid). DNA is the compound molecule that carries the genetic information (blueprint) for most living systems. All members of a species carry virtually identical DNA, meaning that, among humans, every person for the most part has the same genes. But each of us is also genetically unique, and in various places in every person's DNA there are small differences – called polymorphisms – which, together, determine genetic individuality.

The smallest possible unit of DNA is a single nucleotide, one molecule in the string of millions that form DNA. Many differences between people are due to differences in a single nucleotide. This kind of small difference, called a "SNP" (single nucleotide polymorphism, pronounced "snip"), can be detected and analyzed by scientists.

Scientists are now developing the capability to understand the medical significance of some SNPs, for example, linking them to inherited conditions, drug resistance, or disease susceptibility. A collection of different SNPs, when found together, can indicate the ancestry of an individual as well as a particular genetic predisposition. As such, while most SNPs are the same throughout the world, some SNPs are unique to particular populations, for example, a particular indigenous people, a family prone to a hereditary disease, or even regional groups like Africans or Asians.

The Diversity Frontier

A number of groups are rushing to chart the vast, newly opened area of human genetic diversity. First are the private companies, which are beginning to recognize the potential commercial value of genetic diversity. The ability of researchers both to understand the significance of SNPs and, particularly, to apply for patents on them spell considerable trouble for indigenous people and other genetically-targeted research subjects, who are now poised – whether they like it or not – on the cutting edge of genetic research.

The second significant actor in this area is the Human Genome Diversity Project (HGDP), conceived as a worldwide academic undertaking to sequence and store the world's human genetic diversity. The HGDP is distinct from the Human Genome Project (HGP), an international effort to systematically sequence all the genes in the human genome, which has not focused on SNPs. The HGP instead is sequencing an average genome of a 'typical' person. This "typical person" is a compilation of 20 to 30 individuals anonymously selected from hundreds of subjects who, given the demographics of the volunteers used for this project, are thought to be primarily of Western European descent. The HGP, however, is almost finished and anticipates having rough draft of the sequence by the spring of 2000. The HGP expects to have finished sequencing and checking for accuracy the entire genome by the end of the year 2003.[3]

While study and interpretation of the HGPs results will undoubtedly occupy many scientists' time for years to come, the end of the HGP signals a

fundamental shift in the genetic frontier. The scientific machinery set up to sequence an average human genome is now turning to human genetic diversity research. And the commercial potential of that work is beginning to become clear.

Private Companies: The High Stakes Business of Genetic Diversity Research

> *Death is a series of preventable diseases.*[4]
> Dr. William A. Haseltine, Chairman and CEO, Human Genome Sciences

Genetic diversity studies are quickly moving from the highly unsettled "cowboy" frontier, populated by quirky academics and opportunistic "wildcatter" companies, to the settler-phase of the commercial mainstream. Orchid Biocomputer Inc (US), whose clients include SmithKline Beecham, has what the company claims is the highest throughput SNP identification laboratory in the world. According to Dale Pfost, President and CEO of Orchid:

> *The next three years are perhaps the most crucial in the genetics revolution. Orchid will capture the high ground, finding medically important associations that create a whole new range of intellectual property rights."* [5]

Orchid is staking its claim at the US Patent and Trademark Office (USPTO) and its future on the Internet with its website: www.SNPs.com. But even bigger settlers, the major pharmaceutical multinationals, are coming to stay.

For companies, understanding an 'average' genome is much less valuable than understanding its variation. Dale Pfost, president of Orchid Biocomputer, which recently acquired GeneScreen, a top clinical pharmacogenetics services company, emphasizes that value, suggesting that the "… *genetic diversity market is the most rapidly growing market in the healthcare industry, and it is being accelerated by the success of the human genome sequencing program. The next phase of genomics has already galvanized the interests of the entire pharmaceutical industry*…"[6] The amount of money at stake in the race to commercialize human genetic diversity is already huge. Orchid's Dale Pfost estimates that "*the genetic diversity market is now over $1 billion and will continue to increase through the natural outpouring of information from all the sequencing efforts around the world*."[7] But whose genes are used and for whose benefit?

Understanding commercially important variations in the human genome depends on the study of diverse populations. This need for the genes of diverse groups presents special concerns for indigenous peoples and others in the South. These people are already being used as "comparitors" and information sources for the development of treatments and genetically targeted pharmaceuticals (called "pharmacogenetics"). Significantly, many of the genes being sought are for diseases and problems of the wealthy rather than treatments for problems which would benefit the groups being studied. Researchers at Columbia University, for example, discovered a gene associated with baldness in a Pakistani village.[8] The market for products related to hair loss is one of the largest in the world, with consumers in the US alone spending an estimated US$7 billion annually on treatments. The villagers whose DNA is the basis for a patent application, are among the least likely to benefit from a blockbuster drug for baldness.

What's in a Name?
Kiva Genetics takes the "Heart of the Tribe"

Based in San Francisco, Kiva Genetics (kivagen.com) took its name from the Pueblo indigenous people of the US southwest. The company focuses on developing proprietary tools to "*aid in the analysis of genetic sub-populations… with a focus on ultrahigh throughput SNP-genotyping.*" In Pueblo languages, "Kiva" means, "heart of the tribe." The company is busily enabling big corporate researchers to analyze, and potentially patent, the DNA of these and other tribes. While the Kiva name may attract sympathetic attention from liberal Californians, many indigenous people will probably find it sadly ironic and enormously insensitive.

Gene Greed: The Latest US Patent Figures

> *Any company that wants to be in the business of using genes, proteins or antibodies as drugs has a very high probability of running afoul of our patents. From a commercial point of view, they are severely constrained - and far more than they realize.*[9]
> Dr. William A. Haseltine, Chairman and CEO, Human Genome Sciences

There is growing concern that patents on human genetic material are increasing medical costs and restricting access to gene-based products. Instead of promoting innovation, gene patents threaten to stifle biomedical research and hinder competition in an industry that is already dominated by a handful of giant, multinational firms.

As the speed of gene sequencing techniques increases, the commercial stakes grow. Genomics companies foresee the end of the sequencing of the 'normal' human genome by the HGP and are in a frenzy to stake intellectual property claims on genes and polymorphisms as quickly as possible. Genomics companies, never shy, have taken to public touting of their patent applications to bolster investor enthusiasm. In August, CuraGen (US) announced it had identified 120,000 human SNPs. Richard Shimkets, CuraGen's director of "internal discovery" also stated that CuraGen is "*aggressive in making patent filings*" [10] on them. European rival Genset (France) downplayed CuraGen's announcement, but conceded to *Nature*

Biotechnology that "*we need to demonstrate progress to the market.*" [11]

Companies are also filing for patents on the longer DNA sequences. In November 1999, Incyte (US) announced that, to date, it "has filed patent applications covering an estimated 50,000 individual human genes. The company was issued 79 new U.S. patents covering full-length genes during the third quarter, bringing its total number of issued and allowed full-length gene patents to 453."[12] Incyte's success has sparked patent pronouncements from yet other genomics companies.

Celera (US, owned by Perkin Elmer – one of the world's top sequencing machine suppliers) told the press in October that it had filed for "*preliminary patents*" on over 6,500 full or partial human genes - despite Celera's pledge in US Congressional testimony to "only" patent 100-300 human genes.[13] In January 2000 Celera announced that greater than 97% of all human genes are represented in its database, giving Celera coverage of 90% of the human genome. Celera describes itself as "the world's largest DNA data factory."[14]

Not to be left out, Human Genome Sciences (HGS) topped both Incyte and Celera, reporting that it had filed for patents on 6,700 human genes. Moreover, HGS implied that it planned to file more patents using "cookie-cutter" intellectual property software that HGS's CEO William Haseltine calls a "*lawyer in a box.*"[15]

In the majority of cases, the companies have little or no idea about the gene or gene fragment's function. So much for two of the three traditional requirements for patentability: evidence of "usefulness" and an "inventive step." For its part, Celera, as a *Reuters'* correspondent put it, "*is using a 'shotgun' approach, sequencing bits of genes willy-nilly in the belief they will all fit together when they are done.*" [16] Celera and its rivals are not waiting for the pieces to fit together before filing for patents.

Privatizing Diversity: The SNP Caesars ("Seizers")[17]

Company	Partner	Value to Company (if known)	Purpose
deCODE	Affymetrix	?	Gene chip collaboration
	Hoffman LaRoche	$200 million	Collaboration on Icelandic DNA database & SNPs
Genset	Abbott	$62.5 million	Pharmacogenomics, equity investment
	American Home Product	$15 million	Respiratory disorder genetics
	Johnson & Johnson	$4 million	Schizophrenia
	Pharmacia	?	Pharmacogenomics
	SmithKline	?	Equity investment
	Synthelabo	$80 million	Prostate cancer genetics
Axys	American Home Products	?	Human genetic polymorphisms
	Boehringer Ingleheim	$76.5 million	Asthma genetics
	Boehringer Mannheim	$57.3 million	Osteoporosis genetics
	Glaxo	$20 million	Obesity & Diabetes genetics
	Warner-Lambert	$105 million	Schizophrenia & Bipolar Disorder genetics
CuraGen	Biogen	$33.5 million	Database access
	Glaxo	$48 million + *	Database access
	Hoffman LaRoche	$60 million +	Database access
	Abgenix	$15 million	Genomics for cancer and auto-immune disease
Hyseq	Chiron	$34.5 million	Cancer genomics
	Kirin Brewery	$3 million +	Analysis of Kirin's human cell lines
	Perkin Elmer	$25 million +	Gene chip
	SmithKline	?	Human genomics
Genaissance	Telik	?	Estrogen related targets
	Visible Genetics	?	Isogene identification and drug targeting
Perkin Elmer (and subsidiary Celera)	Amgen	$25 million+	Database access
	Aventis (Rhone Poulenc)	?	Pharmacogenomics
	Novartis	?	Database access
	Pfizer	?	Database access
	Pharmacia	$25 million	Database access
Millennium	American Home Products	$100 million	Central nervous system diseases
	AstraZeneca	$60 million +	Respiratory disease genes
	Bayer	$560 million +	Pharmacogenetics
	Becton Dickinson	$51.5 million +	Cancer diagnostics
	Bristol-Myers Squibb	$32 million	Pharmacogenetics
	Eli Lilly	$165 million +	Pharmacogenetics, cancer, atherosclerosis
	Hoffman LaRoche	$76 million +	Diabetes, obesity genes
	Taisho	?	Asthma
Myriad	Bayer	$137 million	Obesity, osteoporosis, dementia, asthma, brain disorder, investment
	Ciba-Geigy	$67 million	Cardiovascular gene discovery
	Monsanto	$15 million	Database/technology access
	Novartis	$67 million	Cardiovascular disease genes, equity investment
	Schering Plough	$64 million	Prostate cancer genes, equity investment

Incyte	AstraZeneca	?	Database access
	Bayer	?	Database access
	Bristol Myers Squibb	?	Database access
	Eli Lilly	?	Database access
	Glaxo	?	Database access
	Hoechst	$15 million	Database access
	Hoffman LaRoche	?	Database access
	Johnson & Johnson	?	Database access
	Novartis	?	Database access
	Novo Nordisk	?	Database access
	Pfizer	$33.8 million	Genomics, equity investment
	Pharmacia	$31 million	Database access
	Rhone Poulenc	?	Database access
	Schering Plough	?	Database access
	SmithKline Beecham	$25 million	Genetic diagnostics joint venture
	Upjohn	$30.1 million	Database access

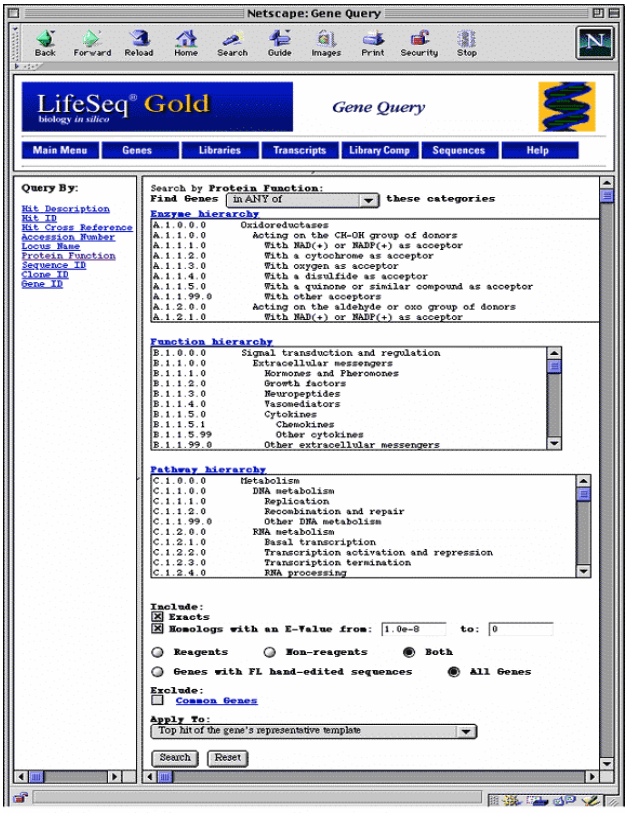
* + indicates milestone payments (amounts provided to companies at various intervals after they successfully meet certain target dates for gene sequencing).

The DNA Databasers

Gene sequencing companies generally seek patents on specific genetic material. However, in the course of sequencing millions of DNA samples, they generate – not incidentally – huge databases of human DNA sequences, including population-specific polymorphisms. An integral part of the companies' business is to sell this data to major pharmaceutical companies, extracting cash to continue sequencing and, if possible, also getting a cut of the profits from commercial products derived from the data.

90% of the Functional Genome at Your Fingertips: Incyte's LifeSeq

With diversity data coming, yours to browse, typically for well over US $1 million a year.



SOURCE: Sample image of LifeSeq from Incyte's website

The database's coverage is extensive. Incyte claims its database contains over 90% of the expressed genes in the human genome. In addition to in-house efforts, all the major pharmaceutical companies subscribe to Incyte's and others' proprietary DNA sequence databases, typically paying well over US$1 million a year per database.

Although some companies deliver copies of their databases on CD-ROM, the industry is quickly moving into electronic commerce over the Internet. When genomics and pharmaceutical companies arrive at a financial arrangement, they create a private, encrypted computer connection between their research facilities, which allows the pharmaceutical company employees to remotely dig into the sequencer's databanks.

Genomics companies are trying to increase the number of subscribers to these databases and have begun to make them more widely available. Hyseq, for example, has recently opened its website "Genesolutions.com," while competitor CuraGen is answering with its "Genescape" Internet site.

At Genesolutions.com, web surfers can sign up, enter a credit card number, and begin searching Hyseq's proprietary database, paying a variable fee per nucleotide accessed. The fee multiplies when the sequences owned by Hyseq's are different from those of public databases holding information on the same gene (i.e. where Hyseq may have diversity data). If a researcher encounters an especially interesting sequence and related data and wishes to obtain a license for the proprietary gene, a US $10,000 charge to a Visa, Mastercard or American Express instantly removes it from Hyseq's online access and earns the researcher a license from Hyseq.

But whose DNA is it? In some cases, companies are holding 'generic' DNA sequences found in one form or another in all of us; but "*genomic research is expanding daily in the direction of genetic variation and how variation relates to function.*" [18] Thus the databases are being filled out - given "high resolution" in industry parlance - with vast quantities of SNP diversity information linked to specific peoples and disease populations. But who precisely? To find out, you must pay up and join

the club. One of Incyte's selling points in its database subscription is the opportunity to: "*Browse cell line and donor information for 895 tissue libraries … in both normal and diseased systems, and at different developmental stages.*" [19]

The information contained on these databases is certainly not available to – or even comprehensible to – the health practitioners that support the "donor" populations. Most do not have access either to a computer or to the Internet, and if they did, the cost of accessing the database is prohibitive. Further, the information contained in the database is presented in a way that makes it difficult for those without an advanced biomedical degree to understand. And most importantly, neither the research subjects nor the healers they trust - have any idea what the database subscribers are doing with the data (including DNA "clone" samples, deliverable on request, for a fee), because the details of company to company arrangements are highly private.

Indigenous Genetic Diversity Internet Sites: Serving Whose Needs?

Companies and other researchers who want to find out about indigenous peoples' genetic diversity don't necessarily have to wait for commercial sequencers to provide information. Academic researchers have been preparing and cataloging human genetic diversity for years. Although the academics' interests may be non-commercial, they are now publishing large amounts of information on the Internet, raising questions about its commercial appropriation.

The increasingly sophisticated genetic profiles of peoples available through a variety of online databases can be used for historic-anthropological work or biomedical research. The diversity data contained in these databases, already patentable, is being supplemented on an almost daily basis. Consider the following examples:

ALFRED: The Allele Frequency Database, at the Kidd Lab at Yale University (US). A rapidly expanding set of detailed genetic data on polymorphism in 65 populations, mainly indigenous peoples, from across the world:

http://fondue.med.yale.edu/db2/index.asp

Human Gene Geography: The as-yet-unavailable, US-government funded "*comprehensive community repository supporting work in human population genetics and quantitative anthropology*." A project of the HGDP team at Stanford University, the database is intended to provide diversity information on 2,000 global populations. While the majority of existing information is based on older protein marker assays, the designers anticipate including SNPs, RFLP information (Restriction fragment length polymorphisms -- the variation between individuals in DNA fragment sizes cut by specific restriction enzymes), and a host of culture-specific data in future versions:

http://crick.stanford.edu/hgg/

HvrBase: Based at the Max Planck Institute in Leipzig and the Zoology Institute of the University of Munich, HvrBase is dedicated to primate mitochondrial DNA (mtDNA). While containing information on baboons, gorillas and other human relatives, HvrBase is mostly dedicated to sequences from indigenous peoples. HvrBase includes mtDNA sequences (previously published elsewhere) on approximately 2,000 indigenous people from over 40 countries:

http://www.zi.biologie.uni-muenchen.de/science/mtdna/hvrbase/

Commercial Diversity Studies in the Field: The Rights of Research Subjects

There are a considerable number of commercial genetic diversity studies currently underway. The commercial race for diversity material is not faceless, but involves the lives of particular groups of people in increasingly alarming ways. The potential violation of basic human rights, particularly with respect to research subjects' health and social well-being, appears to be increasing. Further, in many of the studies it seems likely that researchers are not obtaining fully informed consent from their research subjects. Finally, more general ethical questions about the patenting and commercial use of this genetic material have simply not been adequately addressed. The following handful of examples of genetic diversity studies in the field highlights some of these concerns.

The Millennium Starts Early in China

Genetic diversity researchers at Harvard University, in collaboration with a number of pharmaceutical companies, including Millennium Pharmaceuticals, a biotechnology firm based in Cambridge Mass., have been conducting large scale genetics studies in China. At least 14 projects are underway in China, encompassing as many as 200 million Chinese citizens. The projects include research on obesity, schizophrenia, pulmonary disease, atherosclerosis, hypertension, and colon cancer.

There is a mounting body of evidence suggesting that the rights and protection of the research subjects, mostly located in Anhui Province in China, are being violated (see forthcoming *RAFI Communiqué*). In many cases, the research is being conducted under conditions where proper informed consent is likely not being obtained. The real health risks associated with many of the research studies are

accentuated by a situation where health systems, particularly in the rural areas, have completely broken down due to the changes in the Chinese economy.[20] According to many health workers and other observers, the blood supply is heavily contaminated and syringes and needles are re-used and unsterilized.[21] In many cases, the research is being conducted in China specifically because the population does not have access to modern medicine. The Harvard researchers are not ensuring that their research subjects are provided access to these therapeutic drugs - a situation that would not be tolerated in the US.

In a country where researchers cannot guarantee the privacy of their research subjects, confidential information may lead to prejudiced government authorities having full access to the research data. Serious ethical questions arise in projects that attempt to uncritically capitalize on the poor human rights situation in China, for example, by using the detailed reproductive records of Chinese women. Not least, many of the studies will be of absolutely no benefit to the people being studied - who need a bowl of rice, not gene therapy.

Of Cowboys, Wildcatters and Vampires: The Lesson Drug Majors Never Learned

In the late Sixties and early Seventies, US and European drug companies recognized the commercial profitability of blood. Products extracted from plasma such as albumin, gamma globulin, Human Growth Factor VIII, etc. grew into a multi-billion dollar market that is, today, estimated to be at least US$ 5 billion per annum. The vital raw material for plasma-based drugs was blood. Most of the blood was bought from the college campuses, prisons or skid row slums of the United States but – as demand outstripped supply – it became necessary for the pharmaceutical industry to seek supplies overseas. In an almost totally-unregulated environment, the industry collaborated with blood boutiques (analogous to some of today's biotech or genome boutiques) establishing vampire facilities in the worst slums of Managua (Nicaragua) under the dictator Samosa, in Port-au-Prince (Haiti), under a henchman of Baby Doc, in Mexico, Colombia, and even as far afield as Southern Africa. Destitute families sold their blood at US$3 a litre to brokers who, in turn, shipped it to the four dominant "vampire" pharmaceutical companies in the US. Exposes in the popular press and a campaign by Third World governments and the International Red Cross eventually led to a 1975 World Health Organization resolution that spelled the decline of the gruesome trade. The four ruling US firms were all eventually bought by other, still larger, pharmaceutical giants. France's Rhone-Poulenc acquired Armour, Green Cross of Japan bought Alpha Therapeutics, Cutter was taken over by Bayer of Germany and Hyland became a unit of Baxter Travenol. Yet, as it was a quarter-century ago, it is the same industry and ethics at work collecting human cell lines and conducting genomics research among indigenous peoples around the world today.[22]

Chest Pains in San Francisco

Faced with the intense political problems of sampling diverse populations, some US companies have turned their sights inward. What better way to sample human genetic diversity, without international political strings attached, than to access patients' samples at a large public hospital in immigrant-rich US urban areas? This is precisely the idea that Hyseq, a California-based genomics company, has struck upon. In a collaborative agreement begun in 1998 with the University of California at San Francisco (UCSF), Hyseq and UCSF are collecting and sequencing SNPs and other variations in DNA samples from 20,000 "*genetically diverse individuals,*"[23] all patients at UCSF's affiliated San Francisco hospitals.

In return for an undisclosed amount of money, UCSF researcher John Kane is collaborating with Hyseq to build the huge genetic database that will be owned by the company. Hyseq, in turn, will sell data to its pharmaceutical company clients, as well as develop (and patent) its own medical research on the samples. According to Hyseq, the effort is aimed primarily at finding a cure for cardiovascular disease and is the largest in the world looking at heart-related SNPs. However, samples will likely not be limited to obtaining cardiovascular data, given that " *all the relevant genes from so many samples* [will yield] *a complete genetic picture.*"[24]

The most disturbing feature of the deal is the company's admission that UCSF's detailed patient records greatly enhance the data's value. "*A critical component of this resource is that many of these samples include results from angiogram, ultrasound and biochemical tests, allowing a direct comparison of genetic information with clinical histories.*"[25] While Hyseq assures that the samples are taken by hospital staff with the proper informed consent, there is nothing to suggest that the research subjects are aware that their clinical histories have also been sold or that their genes may be subject to exclusive monopoly patents.

Psychiatric Genetics: Anxiety in Australia makes Bucks for Britain

Gemini Research is a UK company focusing on pharmacogenomic studies of non-identical twins (Gemini means twins in Latin). According to Gemini, the shared age and typically similar environmental factors twins experience growing up makes them helpful in identifying genetic predisposition to disease.

Among Gemini's partners is Australia's Queensland Institute of Medical Research (QIMR). For several years QIMR has been developing clinical data on anxiety and depression in 10,000 pairs of Australian twins and siblings. QIMR's work was greatly aided by the fact that one of its researchers – and

Gemini's collaborator in the commercial agreement – was a founder of the Australian Twin Registry, a national list of twins who are potential volunteers for medical research. In April 1998, QIMR effectively sold its psychiatric data to Gemini for AUS$2.5 million (US$1.6 million).

According to Gemini, the company "*gains exclusive rights to the results of work undertaken to date by the QIMR in* [anxiety and depression and] … *access to a wealth of powerful data in diseases of the central nervous system*," that, according to Gemini CEO Paul Kelley "*will contribute significantly to the scientific and commercial value of the company.*"[26]

Working with "*19 renowned academic institutions,*" including Harvard Medical School, Aberdeen University (UK), St. Thomas' Hospital (UK), and Erasmus University (NL), Gemini is amassing an enormous DNA collection of "*several thousand non-identical twins*" for its private purposes. According to the company, which is already the owner of several patents on human genes, "*Gemini retains biological material from all subjects, offering opportunity to explore new phenotypes as required.*"[27] Although the twin participants may have been willing to consider participating in medical research, it is unlikely, given that Gemini has asserted ownership over their biological material, that they will be given the opportunity to object to any particular uses of their genetic material. This lack of informed consent to specific procedures flies in the face of a number of important ethical decisions affirming the importance of "specific" rather than broad-based informed consent.[28]

Professor Pipeline: Privatizing Academic Genetic Research[29]

SNP/Disease Gene Company	Pharmaceutical/Diagnostic Clients	Academic Data Source(s)
Axys Pharmaceuticals (US)	Boehringer Ingleheim (DE) Boehringer Mannheim Glaxo (UK)* Warner-Lambert (US)	Memorial Sloan-Kettering Cancer Ctr (US) University of Toronto (CA)
Gemini Research (UK)	Affymetrix (US) CeNes (UK) Kyowa Hakko Kogyo (JP) Shield Diagnostics Group (UK)	Erasmus University Medical School (NL) Harvard Medical School (US) Queensland Institute of Medical Research (AU) St. Thomas' Hospital (UK) St. Vincent's Hospital (AU) University of Aberdeen (UK)
Genset (FR)	Abbot (US) American Home Products (US) Johnson & Johnson (US) Pharmacia (SE) SmithKline Beecham (US)* Synthelabo (FR)	Centre d'Etude du Polymorphism (FR) Chinese Academy of Sciences (CN) Royal College of Surgeons (IE) Technion Faculty of Medicine (IL)
Hyseq (US)	Chiron (US) Kirin Brewery (JP) Perkin Elmer SmithKline Beecham (US)*	University of California at San Francisco (US)
Millennium Pharmaceuticals (US)	American Home Products (US) AstraZeneca (UK/SE)* Bayer (DE)* Beckton Dickinson (US) Eli Lilly (US) Hoffman LaRoche (CH)*	Anhui Medical University (CN) Brigham and Women's Hospital (US) Harvard Medical School (US) Massachusetts General Hospital (US)
Myriad Genetics (US)	Bayer (DE)* Monsanto (US) Novartis (CH)* Schering (DE)	Rockefeller University (US) University of Texas (US) University of Utah (US) Valley Mental Health Care (US - Utah)
Orchid Biocomputer (US)	SmithKline Beecham (US)*	University of Cincinnati (US) University of Pennsylvania Health Systems (US) University of Washington (US)

Country Codes:
AU - Australia CN - China IE - Ireland SE - Sweden
CA - Canada DE - Germany IL - Israel UK - United Kingdom
CH - Switzerland FR - France JP - Japan US - United States of America
* Indicates companies which are also members of "The SNP Consortium."

The SNP Consortium: Public Good or Public Relations?

In April 1999, a group of 10 major pharmaceutical companies announced the creation of a public SNP database through a new industry-funded US non-profit organization known as "The SNP Consortium." In describing the rationale for the project, the members state that, through the collaboration, they expect that *"a high-density, high-quality map will be created more quickly, and with shared financial risk and less duplication of effort than if each company pursued development of a SNP map on its own."*[30]

The Consortium has a budget of US$48 million for the SNP mapping. Of this, $33 million comes directly from the 10 pharmaceutical companies and from technology company Motorola, the newest member of the Consortium.[31] The Wellcome Trust (the philanthropic arm of pharmaceutical giant Glaxo-Wellcome) is underwriting the remaining funds. The identification and analysis of the genetic markers (known as single nucleotide polymorphisms - SNPs) will be conducted by a group of collaborating institutions that include the Whitehead Institute for Biomedical Research, Washington University School of Medicine in St. Louis, the Wellcome Trust's Sanger Centre (UK), Stanford Human Genome Center, and Cold Spring Harbor Laboratory.

Members of the SNP Consortium

Wellcome Trust
AstraZeneca PLC
Bayer AG
Bristol-Meyers Squibb
F .Hoffmann- LaRoche
Glaxo Wellcome PLC
Hoechst Marion Roussel AG
Motorola
Novartis
Pfizer Inc
Searle
SmithKline Beecham PLC

The research goals of the Consortium are ambitious. Operating on the assumption that a "working draft" of 90% of the 'normal' human genome will be available by March 2000 from the Human Genome Project (HGP), the gene mapping units of the Consortium aim to identify 300,000 SNPs by the end of 2001. The research will add to the HGP gene maps by providing information not just on the 'normal' human genome but on much of its variability.[32] Once created, the collaborators believe the map will provide direction for *"industry scientists searching for new ways for medicines to cure and prevent disease, and for medicines that more precisely target specific patient groups."*[33]

The Consortium makes much of the public importance of the collaboration. In its statements, Consortium members argue that *"the availability of the map to academic, government, and independent medical researchers worldwide should enable investigation of genes associated with rare diseases, which otherwise might not be feasible because of the significant investment that would be required."* With these statements about how the work is available equally to all, the Consortium also addresses the issue of patenting the material. *"Members of the SNP Consortium believe that a high-quality SNP map will prove to be an essential tool for understanding the genetic basis of disease, and as such, should not be subject to intellectual property restrictions,"*[34] says Arthur Holden, chairman and chief executive officer of The SNP Consortium.

But is industry serious about making diversity public, or is the SNP Consortium something else? Following the money shows that, at best, industry is playing both sides of the SNP "debate." Judged on the basis of where companies are putting their investments, this industry initiative might more accurately be described as an inexpensive way to placate academic researchers and gain public relations points.

The vast majority of pharmaceutical genomics money is going into proprietary approaches. Each of the SNP Consortium members have, on average, given US $3 million to the 'public' effort. All of the pharmaceutical companies who are members of the Consortium have invested many times that amount in private deals with the "SNP Caesars" or on in-house proprietary research. Consortium member SmithKline Beecham is part owner of Genset, Orchid Biocomputer, and co-owns a genetic testing venture with Incyte. Novartis is part owner of Myriad. Others are pouring money into proprietary efforts: German giant Bayer has private genomics deals with Myriad (of which it is also a part owner) and Millennium. Together they are worth approximately US $697 million; 230 times Bayer's estimated investment in the SNP Consortium. Glaxo has signed proprietary deals with Axys and CuraGen worth at least $68 million, 23 times its investment in the Consortium. Other Consortium members AstraZeneca, Novartis, Hoechst, Monsanto, Bristol Myers Squibb, Pfizer, and Roche all support the SNP Caesars by buying access to the proprietary databases (See chart: "Privatizing Diversity," page 4).

While the SNP Consortium claims it will not lay intellectual property claims on the SNPs identified for the project, there is every reason to believe Consortium members will patent therapeutic approaches derived from SNP knowledge, leading to slightly different but still troublesome ethical questions. A *New Scientist* editorial put it well: *" Drugs companies might agree that it is better to share freely information about SNPs but the moment you move 'downstream' towards the point where that information looks like it might yield a promising drug then patents will be flying thick and fast."*[35]

It is possible that, when all is said, done, and patented, the SNP Consortium will be left with the diversity that industry doesn't want, or hasn't bothered to figure out. But, for their paltry investment of $3 million each, the big pharmaceutical companies in the Consortium have tossed a bone to US academic scientists and scored big in public relations.

At the same time, governments have also begun to pay lip service to the importance of public access of genetic material. In September 1999 it was reported that the UK and US governments are negotiating an Anglo-American agreement that seeks to release all publicly-funded research on human genes without claiming patents.[36] The goal of the proposed

agreement is to ensure that the benefits of human genomics discoveries are made freely available worldwide. But without government action to curb private-sector patenting of human genetic material, the proposed Anglo-American agreement is an empty initiative.

Commercial diversity studies are now collecting such a large volume of genetic information in such diverse areas of the world that academic collection activities such as the Human Genome Diversity Project (HGDP) may seem less important. However, they still have their role to play.

The Human Genome Diversity Project (HGDP) Today: Still Besieged, Confused, and in Need of Supervision

The Human Genome Diversity Project (HGDP), a worldwide, academic-led effort to collect, sequence, and store human diversity, gained notoriety in the years after it came to public attention in 1993 (see *RAFI Communiqué* May/June 1993). Resoundingly rejected by scores of indigenous peoples' organizations and rebuffed by UNESCO's International Bioethics Committee (IBC), the HGDP's profile sank considerably after it was deemed unworthy of support (due to ethical and design issues) in 1997 by the US National Research Council.[37]

For years, the HGDP's critics have pointed to a number of problems, including severe internal confusion over project goals, the lack of government supervision, and a series of inadequately addressed ethical issues, including the commercial use of samples, lack of consultation with targeted peoples, and issues relating to the informed consent of research subjects. Little reform in the project has actually been implemented and, instead of engaging its critics as in the past, the Project now hovers below the public radar. The substantive documents about the Project on its website date to early 1990s, while its much-touted Ethical Protocol languishes as a draft. Despite the internal dissent and external pressure, HGDP scientists are resolute in their self-imposed mission and have begun to collect samples in many parts of the world, despite never having put into place measures that effectively address criticisms.

Confused Project Goals

Confusion and distrust about the HGDP stem from early on when project proponents were unable to clarify the goals of the projects and who would benefit from the information. Initially, the HGDP's stated purpose was to broaden study of the human genome beyond the DNA of Europeans and North Americans, and to gather tissue samples that would help geneticists and social scientists trace the early migration of peoples around the globe. The stated goal did not allay the widespread concern by the targets of the HGDP, most of them indigenous people, who feared, among other things, that their genes would be patented for corporate profit. Confronted with questions about whether genes collected by the project could fall under patent monopoly, the project's representatives repeatedly shifted their position on the issue. At first, they gave no consideration to concerns about patenting, claiming that the material had no commercial value. Later, project leaders argued that the project would have important medical benefits, acknowledging that collected tissue samples would *"provide valuable information on the role played by genetic factors in the predisposition or resistance to disease."* Even though they acknowledged the possible medical benefit of the project, they continued to deny that the material would have any commercial value. Nonetheless, they agreed that (in the unlikely event that the material was commercially useful) the HGDP itself would not seek patents. The HGDP went on to declare that if the research did prove to be commercially useful, the peoples involved should benefit financially. Observers found it difficult to keep up with the shifting assumptions embodied in these statements.

Human tissue samples collected by the HGDP will become publicly available for research - not only by HGDP associates, but also by anybody who obtains access to them. Researchers associated with the HGDP must agree not to patent this material or products derived from it. Others will be under no such obligation. HGDP researchers themselves could "re-collect" samples in "non-HGDP" research, and file for patents. In addition to addressing other concerns, the proponents of the HGDP, who are proposing to collect large numbers of human tissue samples, have a fundamental responsibility to ensure that the genetic material collected will not be patented by anybody, before they collect, "immortalize," and make the information publicly available.

Incomplete and Unadopted Ethical Protocol

A well-designed, binding ethical protocol for HGDP researchers might be a step in the right direction. Indeed, the HGDP has drafted such a protocol, saying it answers a wide variety of criticisms. Since 1995, the HGDP has repeatedly touted the protocol as an important protection for research subjects. According to John Moore, a University of Florida anthropologist and Chair of the HGDP North American Committee, *"… we believe* [our Ethical Protocols] *mark the most progressive approach ever taken to human subjects' rights in this kind of research"* (September 1999).[38]

Yet despite such buoyant assertions about ethics, the HGDP has apparently never actually adopted its own protocol. All public texts are labeled "draft," "model," or "proposed." Seeking clarification of Dr. Moore's statement, RAFI researcher Edward Hammond requested a copy of the "*current, official (not draft) version of the Ethical Protocols… to*

which [HGDP has] *adhered"*[39] from both the North American and International committees of the HGDP. There was no response.

Of course there is little place to go but up in terms of ethical measures in human diversity research so the assertion may be correct, although substantial criticisms have been made of the draft version.[40] A critical flaw in the HGDP Ethical Protocol is the lack of external supervision and independent application of sanctions for protocol violations. Further, even if the HGDP was able to adopt a progressive ethical protocol for its own members, they also have a responsibility to address the more fundamental question of what will happen to material that ends up in the public domain. In other words, it's one thing for the HGDP to say that it will not patent any of the material themselves, but if they place the material in the public domain without ensuring that others cannot patent it, they have simply side-stepped their fundamental responsibility to the research subjects.

Imagined Ethical Supervision

The most serious of HGDP's recent transgressions has been to falsely declare that it operates under UNESCO supervision. In July 1997, the HGDP's leadership (partially funded by the US National Science Foundation) made presentations at an international scientific conference in Freemantle, Australia. Dr. Luca Cavalli-Sforza, a Stanford University geneticist and the project's director, told the high-powered group of scientists that: " *The HGDP is under ethical supervision of a UNESCO committee.*"[41]

The statement is incorrect. In reality, the project made a bid for UNESCO support in 1994-95, but failed. Presenting at the 2nd Session of UNESCO's International Bioethics Committee (IBC) (September 1994), Cavalli-Sforza optimistically said: *"The educational, scientific, and cultural importance of this Project, as in the third, fourth, and fifth letters of the acronym of UNESCO, should be clear. We hope that we can establish useful links with UNESCO's International Bioethics Committee to further the Project's important work."*[42]

But the IBC was not convinced. It declined to endorse the project and instead formed a committee to prepare a report on human population genetics for its 3rd session in September 1995. The committee's report, tabled 23 months before the Freemantle conference, rejected the HGDP's request for a UNESCO supervisory committee, noting that an ethical committee on human diversity research should be "*more broadly conceived*" and that "*The claim that the HGDP will reduce racism is debatable."*[43]

An unknown number of scientists from across the world may remain under the false impression that the HGDP has UN backing. RAFI sought from a representative of the project an explanation of its statement. While acknowledging the question, the project's representatives declined to answer. In a communication with RAFI, the IBC confirmed their position with regard to the HGDP.

The Current Status of the HGDP

Given the almost total lack of endorsement by indigenous peoples, civil society, and governments, one would expect that the HGD Project and work envisioned by the HGDP would be halted altogether until some of the ethical and other concerns have been addressed. However, researchers associated with the HGDP have received funding for diversity research and collection of genetic diversity material has proceeded over the objections of its critics. While the number and breadth of collections by the HGDP are far fewer than those held by private companies and non-HGDP academic researchers,[44] the HGDP is gathering funds and collecting without any accountability structure in place.

The Funding Game

"It is amply clear that collections would be premature. Let's get it straight: First we need to see if a project that meets the approval of research subjects can be designed. Then - and only then - can a discussion of funding collections start…"[45]

Alejandro Argumedo, The Indigenous Peoples' Biodiversity Network (IPBN)

Despite the international controversy surrounding the project, according to some members of the HGDP, the project is beginning to have some success in obtaining funding for its activities. In Windhoek, Namibia in February 1999, HGDP International Executive Committee member Trefor Jenkins of the South African Institute of Medical Research (SAIMR) told the delegates of UNESCO's 5th South-North Genome conference that the " *HGDP has been funded in Europe, China, India and, very recently, as a pilot project, in the USA.*"[46]

Despite this remark by Jenkins, whether the HGDP is being funded in the United States is the subject of some debate. Writing to RAFI researcher Edward Hammond in September 1999, John Moore, the Chair of the North American Committee of the HGDP, claimed that " *The North American Committee* [of the HGDP] *still operates on the grant received from the MacArthur Foundation in 1993. We have received no additional funds from anywhere."*[47] However, records of the US National Science Foundation (NSF), which provided over US $1 million in funding to North American HGDP researchers between 1995 and 1997, specifically described some of the work as "Pilot HGDPs." RAFI requested clarification of the contradictions surrounding funding from the HGDP North American Committee and International Executive. None was provided, other than to accuse RAFI of being confused by the important, yet sublime, distinction between the HGDP itself and projects carried out by HGDP researchers who call their

projects Human Genome Diversity Projects, but which are, apparently, not HGDP!

The big issue in the funding debate is whether, in the absence of answers to the ethical and legal questions, the HGDP or its activities should be funded at all. In 1997, following a 30-month review, a committee of the US National Research Council (NRC) advised the NSF against funding the HGDP citing both ethical and scientific shortcomings.[48] The NRC committee that evaluated the HGDP funding proposal concluded that the international collection of human DNA should only take place under the authority of an intergovernmental governance structure. The committee also determined that it would be unethical for scientists to use blood collected from indigenous peoples for any purpose other than that originally agreed to by the research subjects. Indigenous peoples and civil society groups have called for a moratorium on all human biodiversity collecting, unless and until such conditions can be met by the international community. Why any human genome diversity research activities are still being funded in the absence of those conditions has not been answered. The confusion over funding at the HGDP indicates the lack of commitment to integrity necessary for any responsible global survey of human genetic diversity.

Human Tissue Banks in the South

HGDP researchers have also begun to establish human tissue banks housing collections of cell lines, including those of indigenous people. In Argentina, for example, researchers with the Recombinant DNA Laboratory of the Multidisciplinary Institute of Cellular Biology (IMBICE), a government-funded agency, "*maintain a bank of DNA samples that contains over 1500 samples from indigenous populations from North America, Central America, and South America… This bank forms part of the international network of DNA banks of the Human Genome Diversity Project.*" [49]

The location of the gene bank is not surprising, given that IMBICE's head, Dr. Néstor Bianchi, is also the Vice-President of the South American Committee of the HGDP. However, it is unclear why IMBICE is storing North American samples and whether the indigenous peoples represented in the bank are aware their cells have been thus preserved. One possible explanation is that by storing samples in South America, researchers hope to avoid the intense opposition to its work from North American indigenous peoples.

In Africa, the South African Institute of Medical Research (SAIMR) is banking DNA samples collected from many African peoples. Details on the SAIMR bank, headed by HGDP International Executive Committee Member Trefor Jenkins, are unclear; but estimated on the basis of publications from the Institute's researchers on African indigenous peoples, the bank likely contains thousands of samples from dozens of peoples from across Southern Africa (see Box "Bushmen's Loss is Geneticists Gain," pg.12).

HGDP's Internet home page, copyrighted 1999, continues to maintain that the HGDP "*is in the planning stages*" [50] and mentions nothing about an extant international network of human tissue banks. The HGDP seems to have found an important niche for itself. HGDP members can continue to do work of the HGDP while claiming that the project has not begun, and that project funding and gene banks are associated with individual researchers who are simply conducting their own scientific research. However, when it is convenient, for the purposes of credibility and receiving funding, these same researchers claim that their work is part of, or is associated with, this important international project. All without ever having to answer any of the ethical and legal questions that their critics are demanding.

Human Diversity Research: Vignettes

Southern African Bushmen's Loss is Geneticists' Gain

One of the saddest results of the civil wars in southern Africa was the slaughter and dislocation of thousands of indigenous San people (known also as "The Bushmen"). Trapped between sides in the Angolan and Namibian conflicts, in the 1970s and 80s, the San were press-ganged by the thousands into the South African Defense Forces (SADF) at military bases like SADF's "Omega" and "Amigo" camps near the Namibia/Angola border. According to the San, they were threatened with death if they did not join. Still, many of those who agreed to join the SADF wound up dead, often at the hands of the paranoid SADF members.[51]

At the end of the Namibian war, the conscripted San found themselves on the losing side, unwelcome in their traditional homeland, and fearful of retribution by the victors. At least 5,000 San had no practical choice but to move to South Africa with the retreating SADF. Thus the largest concentration of San in Africa has formed around the grounds of the South African military base at Schmidsdrift in Northern Cape Province, where the San are dependent on assistance due to lack of land. Although the new South African government is attempting to find a solution to the problem, the San's situation remains dire.

But for several population geneticists, the San's hardship has been an unprecedented opportunity to sample peoples that are otherwise inaccessible. As early as 1988, researchers from the South African Institute of

Medical Research (SAIMR), headed by Dr. Trefor Jenkins, a member of the International Executive of the HGDP, obtained blood from San conscripts at Omega Base. SAIMR's published results from this work compares genes based on race in the Y(male) chromosome of San and other African populations.[52] According to SAIMR: "*Southern Africa*['s] *people represent three of the major races of mankind, namely, Negroid, Caucasoid, and Khoisan… genetic markers in these populations could confirm, refine, or refute… present theories on the ancestry of these populations and on the admixture between them…*"[53]

In 1994, after the Angolan San had been removed to South Africa, SAIMR returned to sample them at Schmidsdrift. The second time, working with researchers at Pennsylvania State University (US) and John Radcliffe Hospital (UK), the SAIMR published work primarily concerned with an academic debate over the origin of a particular mitochondrial DNA mutation found in some Africans and Asians and its implications for the history of some indigenous populations.[54] The cells have subsequently cropped up in the laboratory of Ken Kidd at Yale University (US), where the San's genetic sequences are being published online and more genetic-historical work is being done. At the Kidd lab, some of the San samples are cataloged as "*Sarah A. Tishkoff's Sekele San sample*" (note the possessive). Tishkoff is a Pennsylvania State University researcher working on historical genetics and malaria who was a visiting scholar at SAIMR in 1997. The samples are also presumably maintained at SAIMR's gene bank at the University of Witwaterstrand in Johannesburg.

Whether the San people gave their consent for the particular uses of their DNA is dubious. What the San think is unrecorded; but it seems unlikely that a people in the San's current situation would find studies on the history of their male chromosomes and mitochondrial DNA particularly helpful.

Science, and the HGDP, marches on as the San slip further toward oblivion.

A Tricky Proposition: Consent from the Dead

In July and August 1976, the US National Science Foundation's research vessel *Alpha Helix* steamed deep into the Brazilian Amazon to collect blood samples from indigenous peoples as far as the Colombia/Peru border. During this expedition and previous studies dating back to the mid-1960s, lead researcher James Neel, a University of Michigan anthropologist, assembled a huge collection of approximately 15,000 frozen blood samples from dozens of Amazonian indigenous peoples.

Using the blood to study the history of peoples, but lacking modern genetic techniques, Neel and colleagues tested red blood cells with protein marker assays. The now antiquated procedure required separating the nucleated white blood cells from the red ones (with no nucleus) and usually throwing the DNA-bearing cells out.

Although modern genotyping of human characteristics became possible in the late 1980s and early 1990s, it became harder to collect samples as some indigenous peoples disappeared and others became more suspicious of genetics researchers. Mindful of the implications for their studies on the "extinction" of indigenous peoples and the cost and political sensitivity of new blood collection projects, some scientists began to focus on "archival" collections such as Neel's. But getting sequence data from most archival samples involved solving a major technical problem. The preserved samples contained little DNA because the white blood cells had been thrown out.

At some point prior to the early 90s, Neel's collection came to rest at Pennsylvania State University (PSU), which has one of the most ambitious genetic diversity research programmes in the US. Researchers at PSU sought a way to revive Neel's collected samples. Because the old blood separation techniques were imperfect, some white blood cells remained in the samples. From these, PSU was able to draw DNA - and lots of it. Using Neel's samples and polymerase chain reaction (PCR), PSU created a technique in which "*the amount of* [genetic] *material that can ultimately be made available is, for many practical purposes, unlimited.*"[55]

The PSU team argued that: "*Whether or not the Human Genome Diversity Project (HGDP) becomes a reality, anthropologists will… want to take advantage of many thousands of existing archival samples, skeletal and tissue collections, ancient bone, and the like that have already been collected, because it is cheaper than trying to resample the existing populations. Of course, many of these populations no longer exist or no longer exist as integral gene pools.*"[56]

The ethical questions raised by the technique are monumental – how can dead *people* grant consent? How can dead *peoples* grant consent? Is it right for geneticists to perform new tests unanticipated at the time of collection? Should they go back to seek permission from the donor, and donor people? If the donor is deceased or gone, should they seek permission from relatives? And what if the people as a whole have disappeared? Parallel to plant *ex situ* collections prior to the Convention on Biological Diversity, whoever has the archival human samples usually makes the decision. The Neel samples holder, PSU, did not consider consultation with Brazilian indigenous peoples necessary.

It is on some of these ethical questions that the HGDP has been called to task, ironically, by the US National Science Foundation (NSF), which funded the *Alpha Helix* expeditions in the first place. NSF's Committee on Human Genetic Diversity concluded that consent for genetic procedures on samples should be specific, not broad. The committee found the HGDP's plans for long-term storage and continued use of samples ethically problematic.

Could the new technology lead to the deception of indigenous people? A 1997 *RAFI Communiqué* report detailed the Colombian *Gran Expedicion Humana* project, which exported blood serum (i.e. red blood cell) samples to the US National Institutes of Health laboratory. In 1997-98, Colombian indigenous peoples and NGOs, including the National Indigenous Peoples Organization of Colombia (ONIC) and Programa Semillas in Bogotá, requested return of these samples, which had been banked and exported without their knowledge. The lead Colombian institution in the project, Universidad Javeriana in Bogotá, initially replied in writing that it would return the samples. But the University later abandoned its written commitment and stated that since the samples sent to NIH were serum, and "contained little DNA," their return was unreasonable and impractical. Yet specialists had known the scientific technique for extraction of DNA from similar samples for over three years prior to Javeriana's rejection of the indigenous peoples request. Why Javeriana had this change of heart is unknown, but could certainly be interpreted as a deliberate attempt to confuse and deceive the indigenous groups affected.

Out-of-Body Experience: How to See the World Without Leaving Home

Among the collections of the *Alpha Helix*'s 1976 expedition were samples from the Tikuna (Ticuna), an indigenous people from Brazil's far west (as well as Colombia). Unlike most of the *Alpha Helix* samples, white blood cell lines were established from Tikuna blood by researchers, including former Human Genome Organization (HUGO) head Sir Walter Bodmer of Oxford University and Julia Bodmer of the Imperial Cancer Research Fund (ICRF), both of the UK.[57]

Although collected nearly 25 years ago, the cells remain in wide circulation among scientists, travelling the world like few, if any, Tikuna have. Among their adventures, the Tikuna cells have been across Europe and the US, and even shipped back to South America to researchers in Argentina. The cells have been used in research for publications in *Genetics*, the *American Journal of Physical Anthropology*, the *American Journal of Human Genetics*, and others. The Tikuna cells have also been incorporated into a major tool for immunology research, the HLA Diversity Cell Panel.

Old stuff? Unlikely, given that, like many *ex situ* plant collections, the cell lines' value seems to appreciate with time. As recently as 1997, Hoffman LaRoche researchers at the company's Roche Molecular Systems division - including the legendary Henry Erlich, one of the creators of polymerase chain reaction (PCR) - were working the cells over and elucidating new information about immunological genetics.[58]

The Tikuna are probably unaware of either their important contribution to science or the potential commercial value of their cell lines. They might not even know about their cell lines at all. If they did, would they approve? Is the work done on their cells in accordance with their culture and wishes? There's no way to know for sure until one of the many scientists using Tikuna cells actually takes the trouble to ask them.

Conclusion

The abuse of the rights of human medical research subjects is the most specious form of BioPiracy. The present failure of national governments and intergovernmental agencies to address these abuses – although not especially surprising – is nevertheless unacceptable. That the regulatory climate has changed not at all since RAFI first warned of these issues early in 1993 is cause for outrage. Over the past seven years, civil society organizations have consistently documented the public and private collection and commercialization of human genetic material around the world. CSOs, and some governments, have raised their concerns in UN and in the media but there has been no useful response from intergovernmental organizations or from scientific institutions. This issue will not go away. Those who fail to respond now will bear the shame later.

At the level of Peoples and Nations:

In the absence of credible engagement with those peoples (indigenous, disabled, or ethnically-targeted) who are of primary interest to those studying human genetic diversity and in the absence of effective international protocols and regulatory mechanisms to govern medical and patent ethics and the cross-border transfer of human genetic material and data, peoples and governments should declare a moratorium on all human diversity collection and commercialization until such agreements are in place;

Peoples, by their own customary practices, and governments by legislation, may wish to establish the collection and/or commercialization of human genomic information without the prior informed consent of the individuals, communities and countries implicated, to be an issue of criminal negligence for which individuals and institutions may be fined or imprisoned.[59]

The serious problem of international documentation of human cell line collections around the world also needs to be addressed. Most of these collections are already in the public domain and available through the Internet. As it exists, the documentation is obscurely defined and extremely difficult to identify by those not expert in the science or the technology. As a result, the information is readily available to the predators of human genetic material, but is almost inaccessible to those who are the targets of such international collection. The management of these databases should come under international governance in a form approved by the target populations themselves. There is a serious debate among target populations as to whether this information should remain as it is in the public domain or should be organized in a format more accessible to the target populations themselves. Given the growing tide of international collections, there needs to be an agreement among target populations about how they want to manage these databases. Several concerned Civil Society Organizations, including RAFI, are anxious to resolve this inequity in database information and access.

At the international level:

- National governments and People's Organizations may wish to explore the possibility of appealing to the International Court of Justice and to the International Criminal Court to defend the human rights of medical research subjects and to bring to justice those countries, companies, and individuals who violate ethical norms;
- The UN Convention on Biological Diversity (CBD) should move immediately to clarify its responsibility with respect to human genetic diversity through an Advisory Opinion from the International Court of Justice via the UN General Assembly or ECOSOC;
- Recalling its pivotal role in controlling the marketing of human plasma in the mid-1970's and the tardiness with which some governments responded to the tainted blood scandals of the 1980's and 1990's, the World Health Organization (WHO) should move immediately to finalize protocols related to the collection and development of human genetic material, including the implications associated with its possible commercialization and claims of intellectual property protection;
- The UN Human Rights Commission and the UNESCO Bioethics Committee should study the issues involved in human genome diversity collection and commercialization and determine the specific steps appropriate to them and to other intergovernmental bodies;
- International professional associations for medicine and the pharmaceutical industry should also study these issues and announce their specific codes and guidelines for evaluation by Peoples and the world community;
- Civil society organizations engaged in human rights and health should add this issue to their agendas and be prepared to cooperate with others in bringing these matters to resolution;
- Governments revising the International Biological and Toxin Weapons Convention in Geneva should evaluate the potential abuse of human genomics research (including their collections and data management) to threaten specific human populations and take appropriate actions to guard against this in the Convention.

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[1] In 1997, UNESCO adopted the *Universal Declaration on the Human Genome and Human Rights* in which it states that "the Human Genome in its natural state shall not give rise to financial gains." However, the Declaration recognizes the authority of international intellectual property regimes and ultimately, in choosing to focus only on the "natural state" of the human genome, completely sidesteps the ethical issues arising from the commercialization and privatization of the human genome.

[2] *The Economist*. 1999. "Genomic Pronouncements." 4 December 1999, p.77.

[3] See Collins, F.S. et al. "New Goals for the U.S. Human Genome Project: 1998-2003." *Science*. 282: 682-689; October 23, 1998, and recent updates on website www.ornl.gov/hgmis/project/timeline.html.

[4] Fisher, Lawrence. "The Race to Cash in on the Genetic Code," *NYT*, August 29, 1999.

[5] "Orchid's New Facility", multimedia presentation available at Orchid Biocomputers website, http://www.orchidbio.com

[6] Orchid Biocomputer, Inc. Press Release. "Orchid Acquires GeneScreen, Inc. January 6, 2000.

[7] Ibid.

[8] Ahmad et al, "Alopecia Universalis Associated with a Mutation in the Human hairless Gene" 279 *Science* (5351), p.720

[9] Fisher, Lawrence. "The Race to Cash in on the Genetic Code," *NYT*, August 29, 1999.

[10] Hodgson, John. "CuraGen lays down markers, 120,000 of them," 17 *Nature Biotechnology*, October 1999, p. 951.

[11] Ibid.

[12] Incyte Press Release, November 22, 1999, *PRNewswire.*

[13] Gillis, Justin. "Md. Gene Researcher Draws Fire on Filings," Washington Post, October 26, 1999, p. E1.

[14] Celera Press Release. "Celera compiles DNA Sequence Covering 90% of the Human Genome." Celera Genomics, Rockville. January 10, 2000.

[15] Fox, Maggie, "Celera Files Preliminary Patents On DNA," *Reuters*, 27 October 1999.

[16] Ibid

[17] Recombinant Capital, http://www.recap.com and Hodgson, John, "CuraGen lays down markets, 120,000 of them." 17 *Nature Biotechnology*, 1999, p. 951.

[18] Quote from Dr. Christopher Hanna of Transgenomic, Inc, a laboratory equipment manufacturer specializing in SNP detection equipment. From Hanna's abstract for a paper presented at a biotech industry meeting on "Implications of Human Genetic Variation," Cambridge, MA, October 1999.

[19] See Incyte's website at http://www.incyte.com/products/lifeseq/lifeseqgold.html

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[57] See *Tissue Antigens* (1980), 16: 152-160.
[58] See *Tissue Antigens* (1998), 51: 41-50.
[59] The notion that the violation of ethical norms surrounding the collection of human genetic material ought to be subject to criminal sanction was suggested to us by Malcolm Dando of Branford University, UK.