# Exhibit Y

#### MEDICINE MERTS VIRTUAL BRALITY II

Interactive Technology & Healthcare: Visionary Applications for Simulation, Visualization, Robotics
Jamary 27-30, 1994, San Diego, California
Spensored by UCSD School of Medicine

PROGRAM COMMITTEE

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December 13, 1993

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TO:

MICHAEL DOYLE PN.D. 415/476.4653

Heime M. Hofbana, Ph.D. Lourning Recurrons Count UCSD School of Mexician

FROM:

Karen B. Morgan

Conference Organizer

Reigh M. Heimet, M.D. Plantic Surpery UCSD School of Medicine

RE:

Your conference participation

Procing J. Kally, M.D. Chief, Newscottery New York Univ. Med. Cor.

Philip I. Marrie apercomputer Center

As of this date, we have not received your:

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Abstract (see letters of September 24 and November 22 for format)

Valore Hamilto, M.D., Ph.D. کے مسالاً عملہ

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> Plaintiffs' Trial Exhibit 725

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#### MEDICINE MEETS VIRTUAL REALITY II Interactive Technology & Healthcare: Visionary Applications for Simulation, Visualization, Robotics January 27-30, 1994, San Diego Marriott Hotel & Marina

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Biomedical Visualization Laboratory at the Unive	moderator): Dr. Doyle is the Principal Investige - ing to UCSF, he was the Director of the costy of Illinois at Chicago. He received his Ph. ity of Illinois at Urbana-Clempergy in 1991. inology and is a past President of The Midwest Mid
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#### Medicine Meets Virtual Reality II: Interactive Technology & Healthcare

#### The Virtual Embryo: VR Applications in Human Developmental Anatomy

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#### The Virtual Embryo: VR Applications in Human Developmental Anatomy

If virtual reality applications in biology and medicine are going to fufill their promise of recreating the subtleties and complexities of biological environments, they must draw from a rich assortment of heterogeneous and highly dense databases containing information about both the structures and functions of the systems to be simulated. This presents a problem for workers in virtual reality, for there are few readily available resources for accurate and detailed data on human biological structure and physiology. Several national-level research initiatives, such as the Visible Human Project and the Human Brain Project, are taking great strides towards creating information resources that can fill this gap. These projects are creating, for the first time, canonical datasets on adult human anatomic topography and topology which will serve as reference datasets for many areas of research into the applications of computer technology to biomedicine. The Visible Embryo project is an attempt to create such information resources for the fields of developmental and molecular biology. It also represents an integrated approach to developing applications of this technology in the areas of image databases, software tools, educational applications, and both basic and clinical sciences. A critical component of this research involves the development of virtual reality applications for research and education in the basic science of human developmental anatomy, as well as surgical simulation tools for practitioners of pediatric medicine.

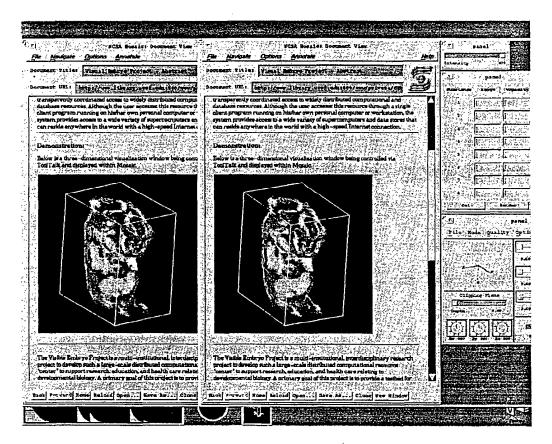
The term "metacenter" was coined several years ago by Larry Smarr, the Director of the National Center for Supercomputing Applications, to propose network-based computing and information "centers that actually represent transparently coordinated access to widely distributed computational and database resources. Although the user accesses this resource through a single client program running on his/her own personal computer or workstation, the system provides access to a wide variety of supercomputers and data stores that can reside anywhere in the world with a high-speed Internet connection.

The Visible Embryo Project is a multi-institutional, interdisciplinary research project to develop such a large-scale distributed computational resource "center" to support research, education, and health care relating to developmental biology. A primary goal of this project is to provide a testbed for the development of new technologies, and the refinement of existing ones, for the application of high-speed, high-performance computing and communications to current problems in biomedical science.

Sets of serial microscopic cross-sections through human embryos, within the collection of the National Museum of Health and Medicine, will be digitized and processed to create volumetric reconstructions of normal human embryonic anatomy. During the five years of this initial project, the entire contents of the Museum's Carnegie Collection of Human Embryology, over 600 embryos, will be digitized, reconstructed and archived, together with case histories, scientific articles, research notes, didactic descriptions, and other data contained within the collection. This massive database will be housed at the Museum at Washington D.C., while teams of researchers at more than 20 universities and companies around the United States will access widely distributed super computing

resources to develop visualization, analysis and telecollaboration software tools, educational materials, virtual reality simulations, basic science investigations, and clinical research projects based upon the data contained within the collection.

This project will serve the dual purpose of providing a testbed for new technology development in high performance computing and communications, as well as creating powerful new tools for the developmental biology research community. New advances in visualization technology are beginning to allow investigators to break through previous technical limitations and discover universally-applicable rules for pattern formation and shape development in organisms. By applying these new technologies to the existing archives of cross-sectional image information that exist in the literature and in collections around the world, we can tap into an enormous amount of new information that can be extracted from these databases.



This image illustrates UCSF's integration of Mosaic documents with remote access to real-time interactive volume visualization tools. The two embryo images are slightly rotated to form a stereo-pair image which can be viewed in 3D by allowing your eyes to diverge slightly so that three images apear, and then focusing in on the middle image (it takes practice). The interactive visualization controls are to the right.

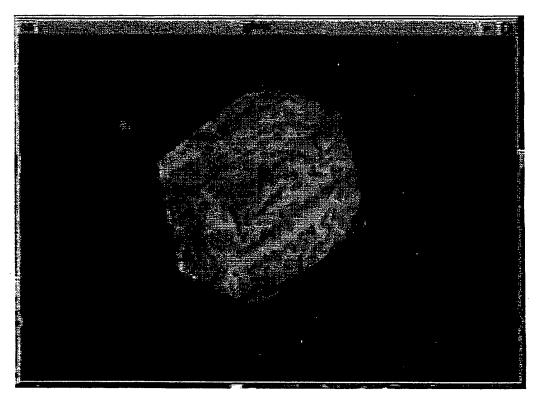
The task of integrating access to such massive information and computational resources is nontrivial. Just one embryo from the 650 serially-sectioned specimens in the collection can yield as much as a terabyte of anatomical volume data (a 20mm specimen, sectioned at 5 microns and digitized at a resolution of 8000x8000 pixels/section at 36bits RGB produces 1.073 TB of voxel data). It is clear that no single workstation, or even supercomputer, can manipulate, process and analyze such a large quantity of data as a single unit, much less perform computational operations on a database of hundreds of such datasets. For this reason, the Visible Embryo team at UCSF has developed tools to allow integrated Internet access (through NCSA Mosaic) to remote volume visualization engines which can distribute computation across a large number of graphics supercomputers connected by high-speed networking. This allows the integration, through NCSA Mosaic and the World Wide Web, of text-based, image, audio, and video data with real-time interactive control of high-performance visualizations embedded within Mosaic documents. We are also exploring the potential of using this technology for delivering interactive access to virtual reality applications through the Internet. The success of these efforts will allow widespread access to highly accurate and complex virtual reality simulations of human developmental anatomy, using inexpensive workstations and personal computers.

M.D. Doyle, et. al., *The Virtual Embryo: VR Applications in Human Developmental Anatomy*, presented at "Medicine Meets Virtual Reality II, Interactive Technology and Healthcare: Visionary Applications for Simulation, Visualization & Robotics," sponsored by the UCSD School of Medicine and the Advanced Projects Research Agency, San Diego, CA, January 27, 1994.

#### **Video Presentation Transcript**:

This is a status report of some of the work that's been accomplished during the first years of the Visible Embryo Project.

One of our first tasks was to develop some volume visualization software that we could use for imaging and analysis of the embryo reconstructions that we planned to create during the full term of the embryo project. One thing that was an absolute requirement was that this software be able to distribute its computational load across a network of graphics computers that weren't necessarily all in the same place. Basically we wanted to be able to have computers that could be all over the country connected by high -speed networking, able to contribute to a computation of three-dimensional datasets.



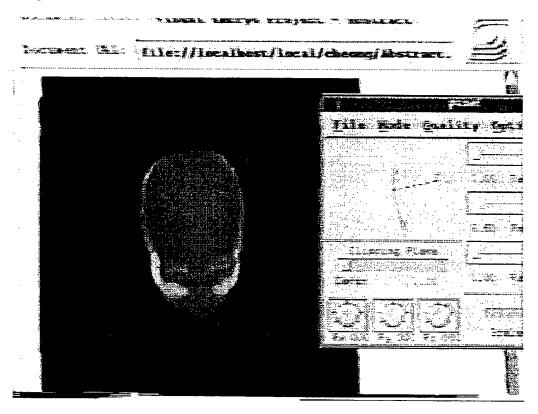
What you see here is a package called "VIS," which was developed in our group, for three-dimensional volume visualization. This is a very portable

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package that has been generated using as generic code as possible, although this particular image that you see here is running on a Silicon Graphics Reality Engine II, which is optimized for volume visualization. We need to use that kind of high-speed optimization to accomplish the real-time interactivity that we need to accomplish for this project. And as you see, as this rotates, and it starts rotating faster and faster, only a very powerful graphics - basically a graphics supercomputer - can accomplish this much computation on a three dimensional dataset. One of our goals is to allow anybody on the Internet with a very low-level access workstation to accomplish this kind of interactivity through their network connection, and the way that we do that is through a client-server architecture where we have a very powerful server computer accessed by a very low-end client machine.

We decided early on to use NCSA's Mosaic program and the World Wide Web to integrate access to this system. One problem with Mosaic is, as it exists today, is that the images within Mosaic are typically static or passive-playback images.

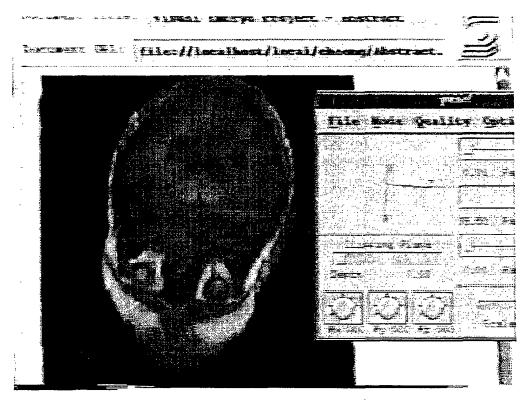


What you see here is an enhancement that we've created to the Mosaic interface and control software that allows the embedding of a dynamic real-time

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visualization application within a Mosaic document. You see a head, a volume MRI model of a human head, that's being rotated in real-time interactively by the viewer. You see a little panel to the right which is, it's a control panel that's popped up - it's really external to Mosaic itself but it can talk to the internal control programs that drive the Mosaic client - and allow you to interactively control the display from within Mosaic. This is actually controlling the volume visualization software that you just saw a few minutes ago.

By moving around the controls in the control panel we can do things like rotate, we can control slices through the dataset, and so on. As you can see, there's rotation in x, y, and z planes. We can also compute arbitrary oblique sections through the data and look at the internal anatomy. Here we can see the brain of this individual; we can rotate and view that section of the dataset from a variety of vantage points. There are zooming capabilities that allow us to zoom up on the data or zoom back to look at things in more or less detail, and you can see here that once zoomed, we're moving our cutting plane down through the dataset and looking at more and more inferior levels.

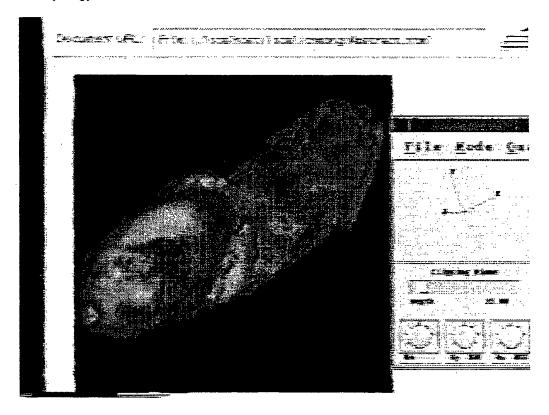


Normally graphics in Mosaic are static, as I said, but this embedding of graphic applications within Mosaic is really going to form the basis of how we integrate information access through the Visible Embryo Project. What you are about to

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see is our prototype system of a Visible Embryo Mosaic document that has embedded realtime visualizations within it.

We just loaded the Visible Embryo Mosaic page, the system is about to scroll down this page - it is an abstract about the Visible Embryo Project - and then we see a window. It looks like a static image just like is normally found within the World Wide Web databases that you can access today through Mosaic, but you can see that suddenly, by moving controls on the control panel, we can zoom in and see that this is a reconstruction of a seven week old human embryo. This is a reconstruction from approximately 2900 serial cross sections of an embryo sectioned about in the 1930s. It's part of the Carnegie Collection of Human Embryology.



We're looking at this in volume visualization mode, we can rotate the embryo around, we can see internal structures, neurological structures; just in the lower abdomen area, we can see the liver, the arms are very evident - so we are actually looking through the dataset. We can also slice through this dataset obliquely, and look at the internal anatomy that way as well. We can load a volume visualization table that allows us to interactively enter tissue characteristic numbers that control the translucency, transparency, or opacity of various ranges of voxal intensity. And what we've done now is we've made the

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exterior of the embryo a little more opaque so that as we rotate around with an oblique cutting plane we can see the difference between the cutting plane and the exterior of the embryo a little better. So now we're looking, slicing - we've rotated the embryo to an inferior view and we're looking up at the embryo from below. And we can see, we've just gone through the heart region, we're going through the liver, we're moving inferiorly and we start to get to an area where we can see the herniated gut.

Now the real key to all of this is that these are embedded visualizations. We're actually creating documents that are - I guess you'd call them currently compound documents where you have the traditional type of information, but you've also got, within that document, links to the raw data rather than just pictures generated from data. This allows you to tie together representations of data with the actual data themselves as well as with notes and different kinds of descriptive textual information based on that data.



Our basic objective here is really to create what we're calling a national metacenter which is going to be a computational resource for the entire nation that allows people interested in many different areas, including developmental biology, also multi-dimensional imaging and high-speed networking, and parallel computing. All these people can access this database. And the parallel

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nature of the computation that's taking place is invisible to the user. They log in through a Mosaic window, and that window is giving them very high-performance control of interactive visualizations of datasets. By scrolling the window, we can see that this is actually embedded within the Mosaic document.

During a recent demonstration of this technology at the corporate briefing center at Silicon Graphics Corporation in Mountain View, California, I discussed some of the implications of this technology for researchers of human genetics.

"We're also looking at using these models as a basis for creating three-dimensional maps of gene expression, which is a way to correlate the findings of the Human Genome project within a context that everyone uses. It sort of sets up a standard space within which everybody can report their findings, so that you can finally have some way of comparing studies that happen in different laboratories.



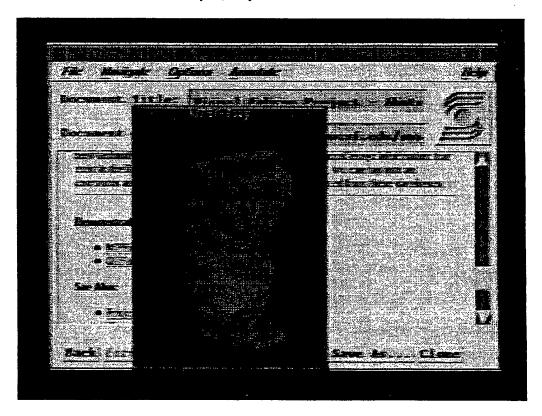
If you're studying the three-dimensional distribution of gene expression of a gene relating to heart development, what you do now is you have a little fluorescent marker that glows under an ultraviolet light, and you use confocal

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microscopy to develop a three-dimensional model of it, and then you say, well, it's on here and it's on there and it's on there and you try to describe it in anatomical terms but it is a qualitative description, right?

But here there would be a standard anatomy space that people could use to describe their findings so that they could, rather than say, yeah, we saw five different studies that said that this was expressed at the bifurcation of the aorta with the Common Carotid artery - you don't have to do in terms of verbal descriptions, you can do it in terms of a true measurable Cartesian coordinate system.

If you take your current version of Mosaic, the kind that is accessible for free through the Internet today, and log onto our home page of the Visible Embryo Project, what you'll see is a series of multi-media documents that basically give you information about the status of the Visible Embryo Project and the status of our current proposal development efforts. You'll be able to load MPEG movies of visualizations of human embryos, as you can see here.

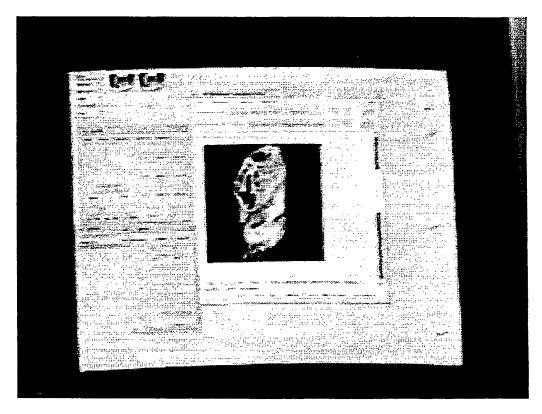


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One thing you should keep in mind is that this little MPEG movie is just a canned movie, it's not interactive. Once you hit Play it just goes and it plays and then it goes away, but you can't stop it and interact with it, and rotate that embryo, for instance, to different vantage points.

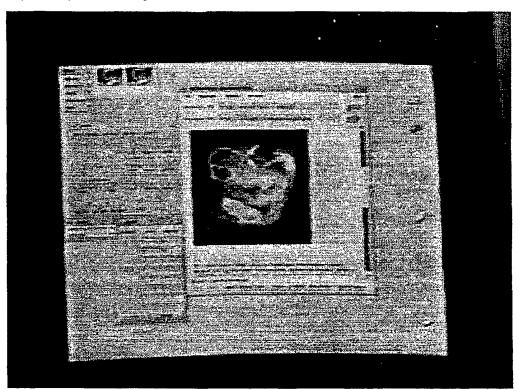
Also available is an image that shows some of the early work, some screen shots representing the volume visualization tool current as of about last summer. We've come much farther and in fact a lot of the video that you saw earlier in this presentation shows you the current status of this volume visualization package. Last summer, that imaging package was separate from Mosaic, as you see it's off to the right, and Mosaic could just call it but couldn't actually embed visualizations. Now, everything is tied together into a single multi-media document.

You'll also see articles that relate to the Visible Embryo Project. This project has been going on for several years now, mostly on the coattails of other research projects, collaborators funding it wherever they could find the money. But already a significant body of literature is starting to be built up around this project.



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Of course, in the very near future, you'll be able to log on through an enhanced version of Mosaic. We're working together with the National Center for Supercomputing Applications on enhancing the standard release of Mosaic to allow these capabilities. And you'll be able to access interactive dynamic visualizations that are being served by a network of high-end supercomputers across the country. Even if you're only accessing the system with a machine like a Macintosh or PC, you'll still be able to access the power of these supercomputers from your own location.



What I've attempted to demonstrate in the last several minutes in this presentation is that there's been a considerable amount of work already done in this project that we call the Visible Embryo Project. Many collaborators across the country have worked together to create a set of enabling technologies to allow this project to accomplish its goals. The Visible Embryo Project represents an effort to serve the needs of both the biology community as well as the information science community, in that we are attempting through current applications in information technology to break through barriers that have prevented biological researchers from asking and answering questions about the most fundamental mechanisms of human growth and development. We're also creating a technology development testbed for the information sciences that will allow researchers to push the envelope, so to speak, of information technologies to their very limits.

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## MEDICINE MEETS VIRTUAL REALITY II INTERACTIVE TECHNOLOGY & HEALTHCARE January 27-30, 1994

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With Special Thanks to Anita Hampton for her help in the preparation of this publication

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troversies regarding the somatotopic organization of the motor system by capitalizing on the fine spatial resolution of fMRI; applied fMRI to the study of cortical and subcortical interactions involved in motor learning/plasticity; and addressed issues regarding cerebral dominance for movement control and speech. Our long range goal is to establish fMRI as a diagnostic tool to complement existing invasive technologies. Supported by McDonnell-Pew Program in Cognitive Neuroscience. [Collaborators: Jeffrey R. Binder, Peter A. Bandeuini, Thomas A. Hammeke]

Kantl Ugurbil (Univ of Mimnesota)

"Functional Imaging with Magnetic Resonance: Cognition"

Monday, 2:30pm

H/Continental Ballroom 4

### Imaging Systems for Health Education and Health Care Delivery

Organized by: Michael J. Ackerman (Natl Library of Medicine, NIII)

Sponsored by AAAS Section on Information, Computing, and Communication

This session is designed to demonstrate through the description of ongoing projects, the broad impact that digital imaging technology is having on health education and health care delivery. The National Library of Medicine's Visible Human Project, the development of a digital anatomical database, will change not only how anatomy is taught but also how surgeons are trained by serving as the data source for the development of artificial reality surgical environments. The Armed Forces Institute of Pathology's Visible Embryo Project, the development of a digital embryology database, will lead to a greater understanding of human developmental biology, both in time and space. Imaging research at Stanford University has led to the fabrication of exact replacement prosthetic devices for bone, joint and even ear replacement, and the preplanning of surgical procedures. A library of digital medical images stored at the University of Washington is now accessed in seconds via the Internet by students across the United States as reference material for studying anatomy, pathology and radiology. The impact of the application of the digital imaging techniques used in Lucas and Disney films on the health education of the student, practitioner and patient is just beginning to

## Michael J. Ackerman (Natl Library of Medicine, NIH) "The Visible Human Project"

The National Library of Medicine (NLM) has long been a world leader in the archiving and distribution of biological and medical print-based images and a pioneer in the use of computer systems to encode and distribute the textual knowledge of the life sciences. NLM's Long Range Planning effort of 1985-86 foresaw a coming era where NLM's hibliographic and factual database services would be complemented by libraries of digital images, distributed over high speed computer networks and by high capacity physical media. The NLM Planning Panel on Digital Image Libraries in Biology and Medicine recommended that NLM undertake the building of an initial digital image library of volumetric data representing a complete normal adult human male and female cadaver. This "Visible Human Project" would consist of the collection of digital images derived from computerized tomography, magnetic resonance imaging, and cryosectional photographic images. The Visible Human

Project data set will comprise approximately 42 gigabytes of uncompressed pixel data, enough to fill over 70 CD-ROMs. It serves as a comeratione for future sets of related image libraries and as a test platform for developing high performance computing and communication imaging, rendering and analysis methods and standards. In order to facilitate retrieval, methods need to be developed to link image data to symbolic text-based data which includes names, hierarchies, principles and theories. Basic research is needed in the description and representation of structures, and the connection of structural-anatomical to functional-physiological knowledge. This is the larger, long tern goal of the Visible Human Project: to transparently link the print library of functional-physiological knowledge with the image library of structural-anatomical knowledge into one unified resource of health sciences information.

Michael D. Doyle (Univ of California-San Francisco)

"The Visible Embryo Project: A National Metacenter for Developmental Anatomy"

The term "metacenter" was coined several years ago by Larry Smarr, the Director of the National Center for Supercomputing Applications, to propose network-based computing and information "centers that actually represent transparently coordinated access to widely distributed computational and database resources. Although the user accesses this resource through a single client program running on his/her own personal computer or workstation, the system provides access to a wide variety of supercomputers and data stores that can reside anywhere in the world with a high-speed Internet connection. The Visible Embryo Project is a multi-institutional, interdisciplinary research project to develop such a large-scale distributed computational resource "center" to support research, education, and health care relating to developmental biology. A primary goal of this project is to provide a testbed for the development of new technologies, and the refinement of existing ones, for the application of high-speed, high-performance computing and communications to current problems in biomedical science. Sets of serial microscopic cross-sections through human embryos, within the collection of the National Museum of Health and Medicine, will be digitized and processed to create volumetric reconstructions of normal human embryonic anatomy. During the five years of this initial project, the entire contents of the Museum's Carnegie Collection of Human Embryology, over 600 embryos, will be digitized, reconstructed and archived, together with case histories, scientific articles, research notes, didactic descriptions, and other data contained within the collection. This massive database will be housed at the Museum at Washington D.C., while teams of researchers at more than 20 universities and companies around the United States will access widely distributed supercomputing resources to develop visualization, analysis and telecollaboration software tools, educational materials, virtual reality simulations, basic science investigations, and clinical research projects based upon the data contained within the collection. This project will serve the dual purpose of providing a testbed for new technology development in high performance computing and communications, as well as creating powerful new tools for the developmental biology research community. New advances in visualization technology are beginning to allow investigators to break through previous technical imitations and discover universally-applicable rules for pattern formation and shape development in organisms. By applying these new technologies to the existing archives of cross-sectional image information that exist in the literature and in collections around the world, we can tap into an enormous amount of new information that can be extracted from these databases. [Co-author: Adrianne Noe, Armed Forces Inst of Pathology)

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Parvati Dev (Stanford Univ) "Imaging and the Custom Fit"

James F. Brinkley (Univ of Washington) "The Digital Anatomist Project"

The long term goal of the University of Washington Digital Anatomist Project is to develop methods for representing, generating, and utilizing structural information at levels ranging from gross anatomy to molecules. In order to approach that goal we are developing the Digital Anatomist framework, a distributed architecture in which a set of client programs access and contribute to an expanding database and knowledge base that includes anatomical terminology and semantic relationships, textual descriptions, 2-D medical images, and 3-D reconstructions. An example client program is the Digital Anatomist Browser, which runs on a low cost Macintosh and accesses the structural database over the Internet. A cross-continental demonstration project between the National Library of Medicine and Scattle shows the potential for multi-media information retrieval, in which low cost desktop workstations can be connected over the emerging "information superhighway"

to high quality medical image databases. [Collaborators: Kraig Eno, John Sundsten-4 and Cornelius Rosse].

Alvy Ray Smith (Altamira Software Co.) "A Glimpse at the Future of Medical Imaging"

Computational power is increasing so fast at low cost that many of us find it difficult to know what is available today, much less see ahead. Nevertheless, I will attempt to predict the future, with dates, of imaging in general and medical imaging in particular using conservative estimates. I will distinguish between geometry-based graphics and sampling-based imaging and use the National Library of Medicine's Visible Human Project "Adam and Eve" database as a hard example.

Monday, 2:30pm

H/Teakwood A-B

#### Social, Ethical, & Scientific Perspectives of Biological Research on Sexual Orientation

Organized by: Rochelle A. Dlamond (National Organization of Gay & Lesbian Scientists & Technical Professionals) and Amy A. Ross (National Organization of Gay & Lesbian Scientists & Technical Professionals)

Recent scientific research has identified possible biological and genetic correlates of male homosexuality. While no study to date has conclusively shown that sexual orientation is heritable or determined solely by biological diversity, the available data do indicate that at least part of human sexual orientation may have an immutable component. As with all biological research, along with the potential to help comes the potential to harm. This session will critically examine the existing data on the biological correlates of homosexuality. Does the influence of nature outweigh that of nurture or does environment play a key role in the regulation of behavior to produce an individual's sexual diversity? Further, the session will address the social, psychological, and ethical implications of these and future findings. Historical and contemporary realities in regard to how genetic technology will be applied in this area will be discussed. Human rights, personal privacy, and social tolerance in light of such scientific data are current topics of debate. It is important that issues involving information gained from such research be discussed openly and allow for the evolution of sound policy to progress as the scientific research progresses.

Dean Hamer (National Cancer Inst)

"Genes, sexual orientation and ethics"

Human sexuality is too complex and variable to ever be explained by any single factor. Nevertheless, recent experiments, including those carried out in my laboratory, suggest that genes and other biological components play a significant role. This presentation will examine the evidence that sexual orientation is influenced, but not determined, by genes, including a locus on chromosomal region Xq28 that is correlated with homosexual orientation in some men. Of concern is the possibility that such information, despite its inherent lack of predictive power, might be misused to discriminate against people based on their genetic makeup. Of equal concern is the possibility of raising unwarranted fears and suspicions concerning all biological research on sexual behavior. The AIDS epidemic has taught us, too bitterly, that we have more to fear from ignorance than from new knowledge about human sexuality. The historical record suggests both that biological explanations of behavior can be used to stigmatize and discriminate and reveals that most such accounts of behavior have been scientifically wrong. Some of this research was conducted with good intentions, but it led to such outcomes as eugenic sterilization and racist immigration restriction. The historical record indicates that recent research in the biology of sexual orientation should be treated with strict scientific reservation and social caution. Like earlier biobehavioral research, some of its methodology is questionable; its scope is limited; and it may well prove to be mistaken. Although it has been hailed in some quarters as possibly providing leverage for gay rights, it could be used to pathologize homosexuality and exploited by conservatives to limit those rights, perhaps severely.

Daniel Kevles (California Inst of Technology) "Historical Politics of Biobehavioral Research"

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Laura S. Allen (Univ of California-Los Angeles)

"Anatomical and Physiological Correlates of Sexual Orientation"

The process of sexual orientation of the brain has been studied in many nonhuman species. During early development, levels of gonadal hormones determine whether the brain develops in a stereotypically feminine or masculine direction in terms of a number of sexually dimorphic structures and functions. As a result of this early hormonal influence, there is a correlation between various sexually dimorphic brain characteristics. The role of gonadal hormones in influencing the developing human brain is unknown. However, recent research suggests a correlation between sexually dimorphic