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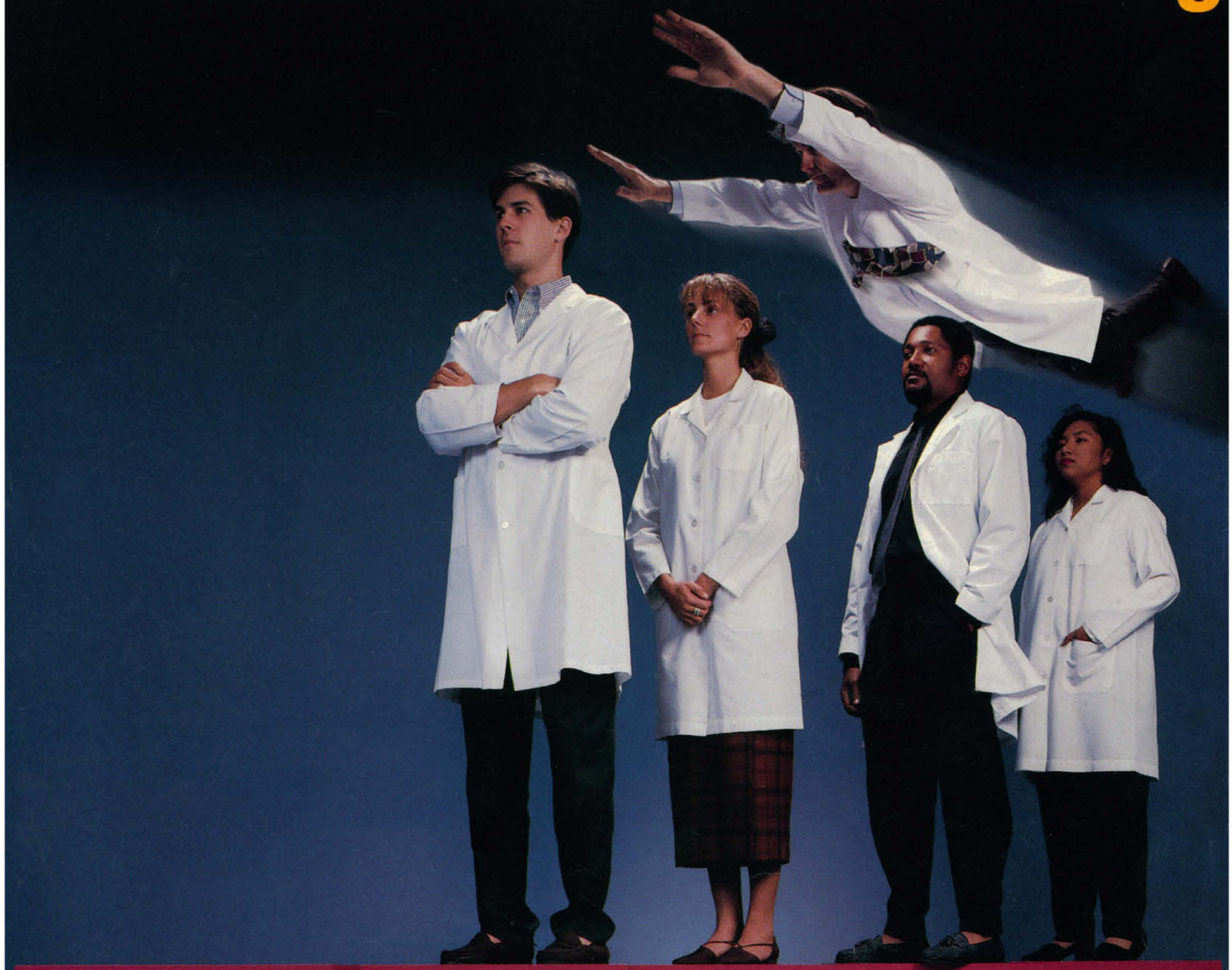
Frontiers in Biotechnology

Antibiotic Resistance

A BOLD LEAP in Cloning



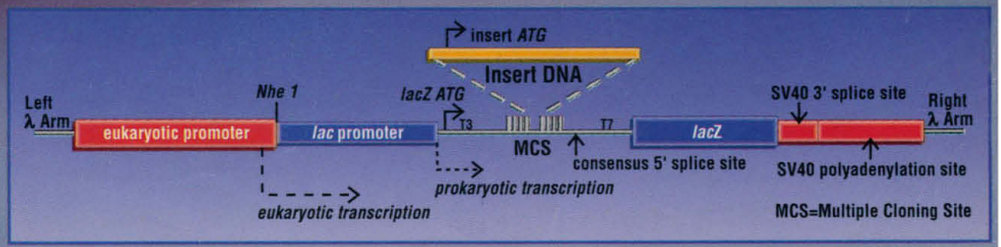
lambda ZAP Express/pBK

lambda ZAP/pBluescript

lambda phage

filamentous phage

plasmids



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* U.S. Patent No. 5,128,256

References:
1. Alting-Mees, M.A., et al. (1992) *Strategies.* Volume 5, Number 3.
2. Alting-Mees, M.A., Vaillancourt, P., and Short, J.M. (1993) "Phagemids and Other Hybrid Vectors" in *Plasmids A Practical Approach* (K.G. Hardy, ed.) pp 197-223.
3. Short, J.M., et al. (1988) *Nucleic Acids Res.* 16: 7583-7600.
4. Short, J.M., and Sorge, J.A. (1992) *Methods Enzymol.* 216: 495-508.

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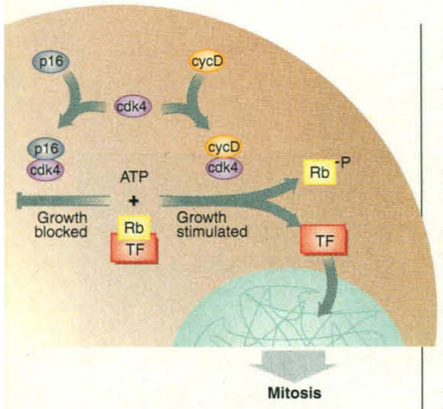
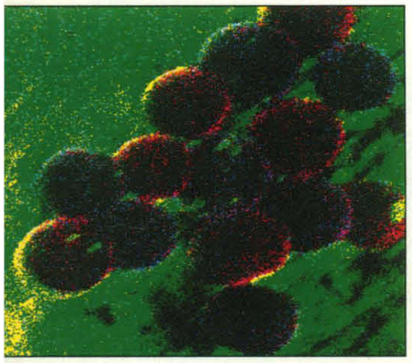


344 & 436
Cell cycle inhibitor may be tumor suppressor



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COVER

Keeping pace with the ability of bacteria to become resistant to antibiotics is a challenge for the clinician and the researcher. This special issue focuses on antibiotic resistance in bacteria: How does it work, and where does it come from? Bacteria have at their disposal several ways of developing resistance. The cover illustrates a low-permeability outer membrane barrier, an antibiotic-efflux pump, and gene transfer. See the special section beginning on page 359 and a related report on page 418. [Illustration: Katharine Sutliff]

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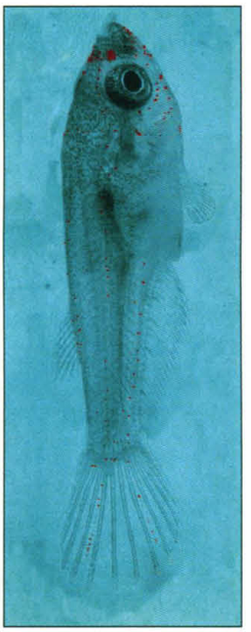

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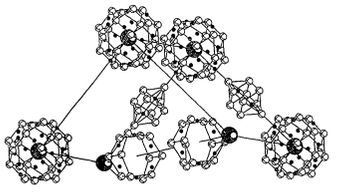
THIS WEEK IN SCIENCE

edited by PHIL SZUROMI

Cluster couplings

Studies by Wang *et al.* (p. 402) of some unusual copper oxide clusters give some insight into the effect of bond geometry on the magnetic interactions between copper spins. They used bulk magnetization measurements and magnetic neutron diffraction $BaCuO_{2+x}$, which has a large unit cell in which the copper atoms exist as lone ions, as 6-atom ring clusters, and as 18-atom spherical clusters. The clusters, which have Cu–O–Cu bond angles near 90°, have ferromagnetic ground states. In the parent compounds of the high-temperature superconductors, where the Cu–O–Cu bond angles are near 180°, antiferromagnetic coupling is observed. Buckling of CuO_2 planes may influence the magnetic ordering in high-temperature superconductors.



Rules of iron

Earth's iron-rich outer core is molten, whereas the inner core is solid. The phase relations of iron at high pressures and temperatures are critical for discerning the conditions and evolution of Earth's deep interior. Recent diamond-anvil studies suggest that the melting temperature of iron at high pressures was less than that inferred from earlier work. Saxena *et al.* (p. 405) present new data consistent with this result and use the expanded data set to place limits on core temperatures and iron phase relations, which imply that the central core temperature is about 6150 K.

Cell cycle regulation and tumorigenesis

General strategies for developing antitumor drugs require the identification of oncogenes or tumor suppressor genes common to many types of transformed cells. Cell cycle regulators are natural candidate genes in that uncontrolled division is a common feature of cancer cells. Kamb *et al.* (p. 436; see news story by Marx, p. 344) localized a putative tumor suppressor locus on the short arm of chromosome 9 (the human 9p21 region) to a region of less than 40 kilobases by examining homozygous deletions in melanoma cell lines. Sequencing revealed the presence of a gene, Multiple Tumor Suppressor 1 (*MTS1*) that encodes the previously identified p16 inhibitor of cyclin-dependent kinase 4. This gene was found to be homozygously deleted in primary tumors and in cell lines derived from tumors in numerous tissue types, including brain, bone, skin, and kidney. Melanoma cell lines containing at least a single copy of *MTS1* frequently carried mutations in the gene.

Air brakes

Geodesy from space is accurate enough to allow changes in the Earth's rotation period to be measured with almost microsecond accuracy, and at this temporal level variations due to the transfer of angular momentum between the body of the Earth and the atmosphere start to show up. Salstein and Rosen (p. 407) combine length-of-day measurements with calculations of the atmospheric angular momentum based on wind and air pressure data to show that weather systems in mountainous regions are largely responsible for the dynamical link between Earth and its atmosphere. Torques along the north-south ridge of the Andes are particularly important.

Not really stable

Planetary atmospheres are marked by global circulations and local vortical motions, but it has been thought that in a suitably long-term, spatially averaged sense, atmospheric fluid flow patterns are isotropic. McWilliams *et al.* (p. 410) performed high-resolution computer simulations of a representative cubical box of a typical planetary atmosphere. They found that although vortices initially form and move about in a random or chaotic manner, giving the illusion of statistical isotropy, the system evolves to long-term stability marked by the localization of vortices into a fixed geometrical arrangement.

Putting up magnetoresistance

The electrical resistance of some materials changes as a magnetic field is applied, in some cases by orders of magnitude. This giant magnetoresistance (GMR) effect is of intrinsic physical interest but is also being explored for applications in magnetic data storage. Jin *et al.* (p. 413) fabricated epitaxial La-Ca-Mn-O films that exhibit magnetoresistance ratios at 77 K that are three orders of magnitude greater than those of conventional GMR materials. The films were made by laser ablating a target of La-Ca-Mn-O onto an $LaAlO_3$ substrate. The film growth could be optimized to produce a magnetoresistance ratio greater than 100,000 percent. The authors conclude that the mechanism for this effect in these single-phase oxide films is different from that in GMR. Better control of the material processing may make these films technologically useful.

Higher frequency

The frequency of polyploidy in angiosperms has been estimated by various means to be between 30 and 70 percent. Masterson (p. 421) has reexamined the question by studying the size of guard cells in fossil angiosperms. Because DNA content varies directly with guard cell size, they are able to estimate that 7 to 9 is the primitive haploid chromosome number. By extrapolation, 70 percent of extant angiosperms have polyploid origins.

Microsatellite images

Microsatellites are tandem repeats of short nucleotide sequences and are present in thousands of copies dispersed throughout the mammalian genome. The variation in the size of microsatellites has been useful for researchers who map genomes as a source of restriction fragment length polymorphism. Gaillard and Strauss (p. 433) report that double-stranded DNA fragments containing one of the most frequent microsatellite sequences spontaneously associate into four-stranded structures that appear X-shaped under the electron microscope. Such four-stranded structures have been suggested to participate in recombination and in conformational changes in DNA. In addition, these structures bind specifically to the abundant nuclear proteins HMG (high mobility group) 1 and HMG 2 whose functions are unknown.

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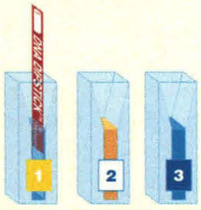

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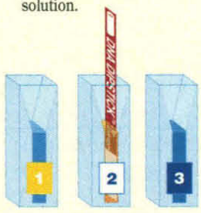
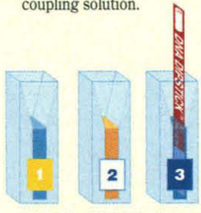


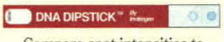
6 Min.

Transfer the DipStick to coupling solution.



10 Min.

Wash the DipStick, then transfer to the developing solution.



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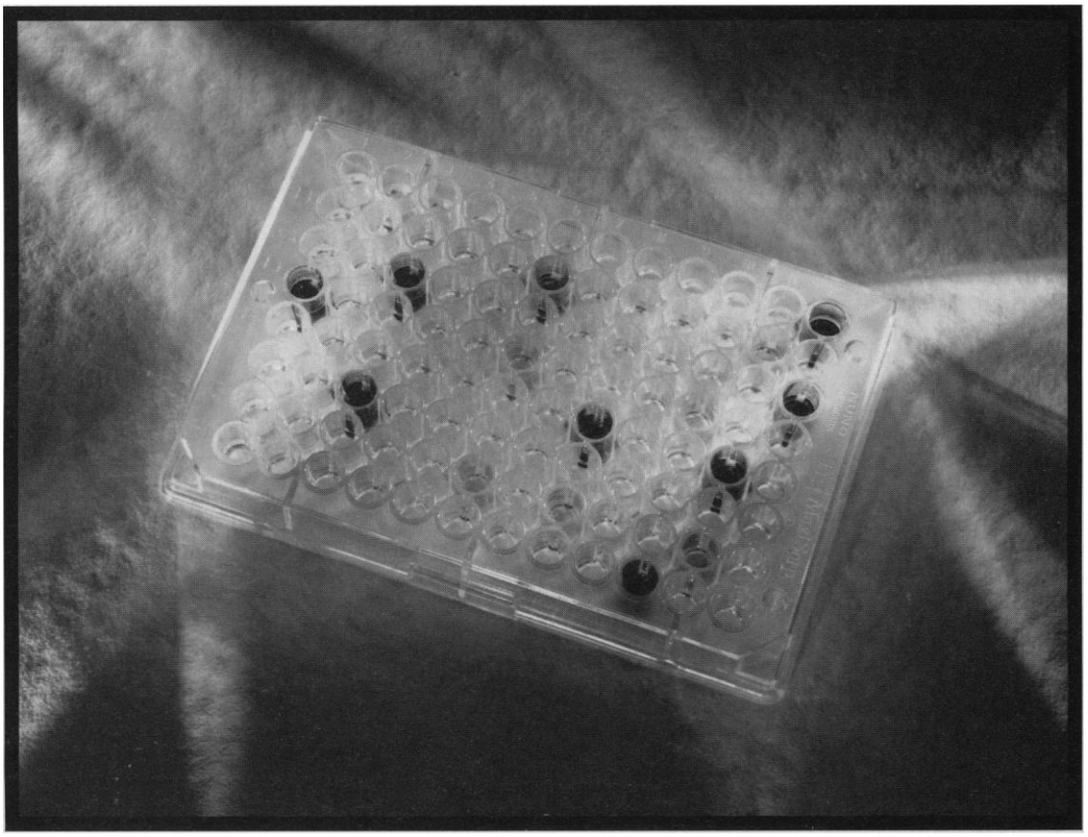

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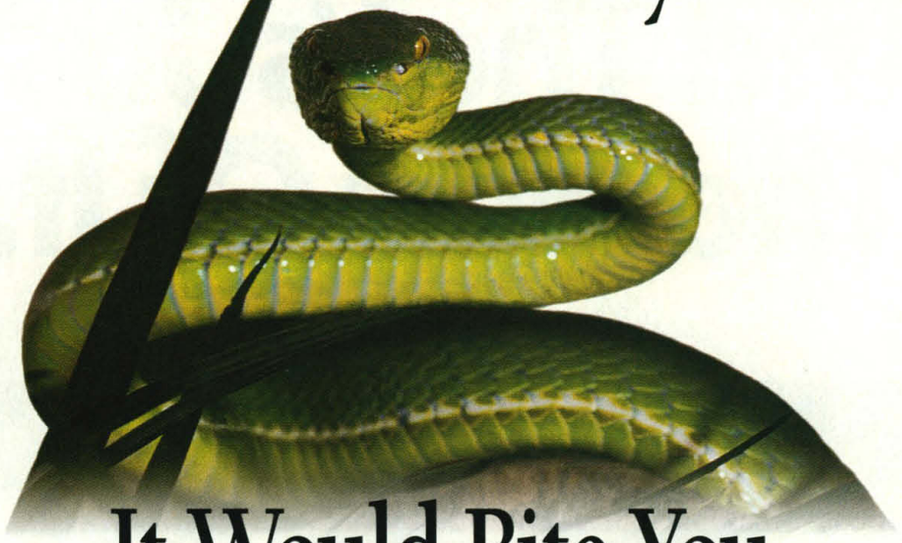

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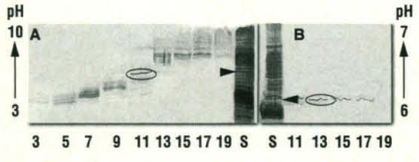
The New Rotofor® System is the Solution to Any Purification Challenge

With the New Rotofor system, any biologically active protein can be completely purified from crude or partially purified samples in just a few hours. Fractions can be assayed directly for activity, so there is no need to know the isoelectric point or molecular weight of a protein prior to purification.



Crude snake venom (150 mg) was fractionated in the Standard Rotofor chamber (60 ml; pH range 3–10). The protein of interest was isolated in three fractions which were refractionated in the Mini Rotofor chamber (18 ml; pH range 5–7). Twenty fractions from both runs were analyzed for purity by silver stained IEF-PAGE. **Panel A.** Initial fractionation (odd lanes are shown). Lane S. Crude snake venom (arrows indicate protein of interest). **Panel B.** Refractionation resulting in single band purity.

What better tool is there for purifying uncharacterized proteins for sequence analysis, antibody production, or crystallography? None!

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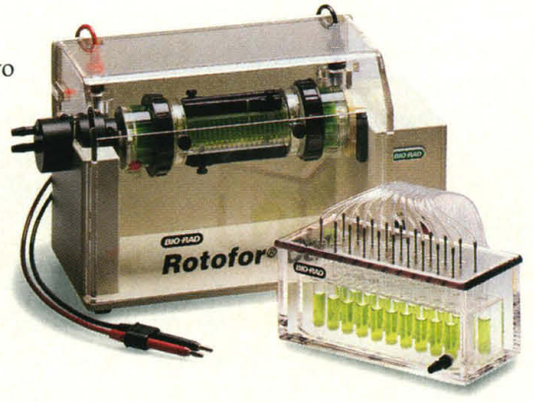
We have the antidote! For more information about purification of snake venom proteins and other Rotofor system applications, call 1-800-4BIORAD.

Introducing the New Mini Rotofor Cell

The Rotofor system now has two interchangeable focusing chambers–Mini and Standard. Together these chambers accommodate a wide range of sample volumes. The Mini chamber is ideal for small samples and refractionation.



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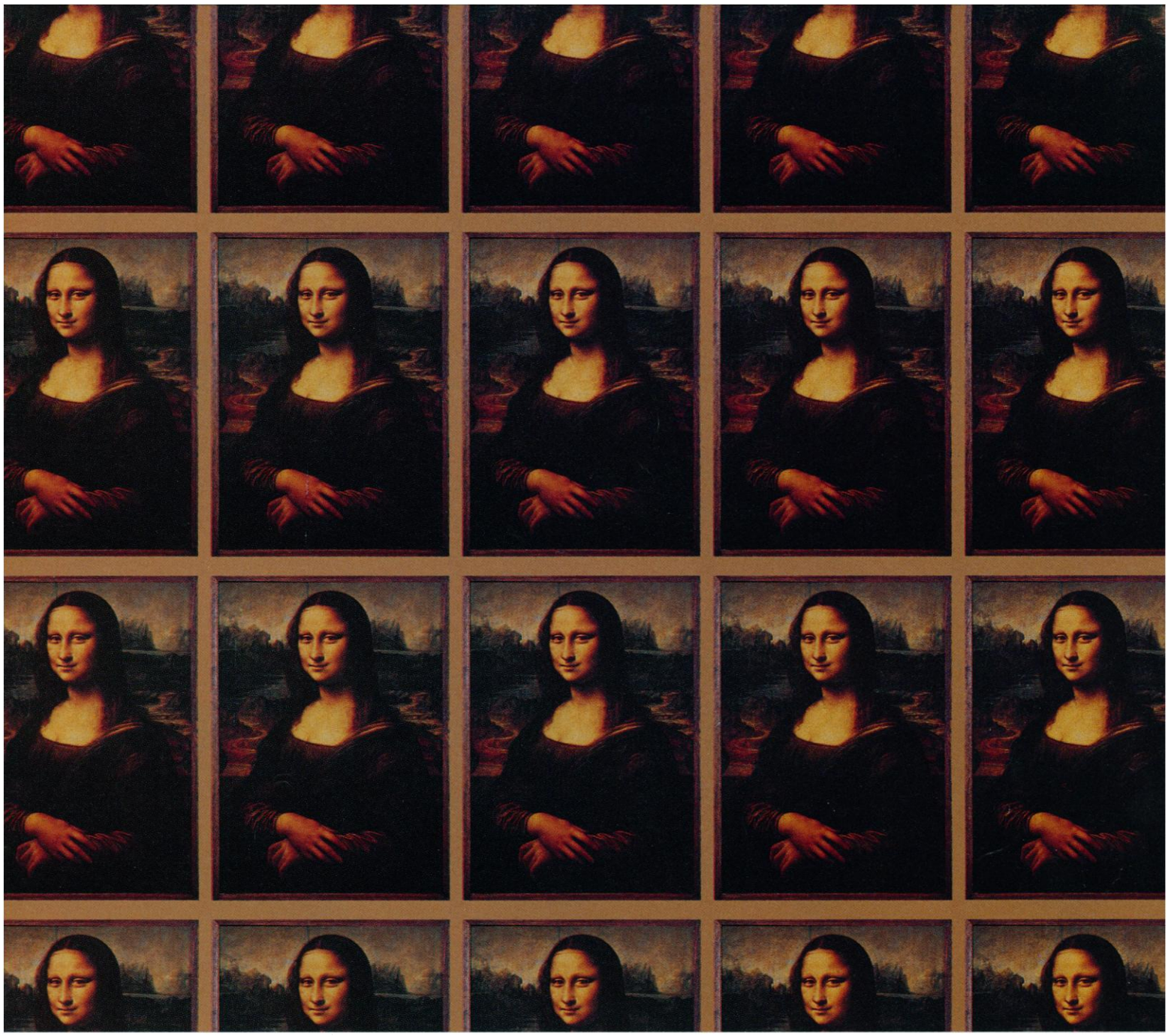

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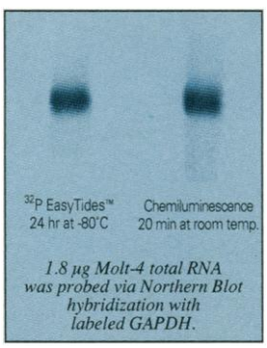

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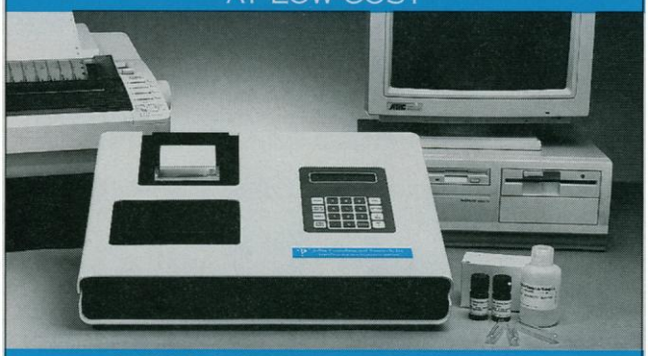

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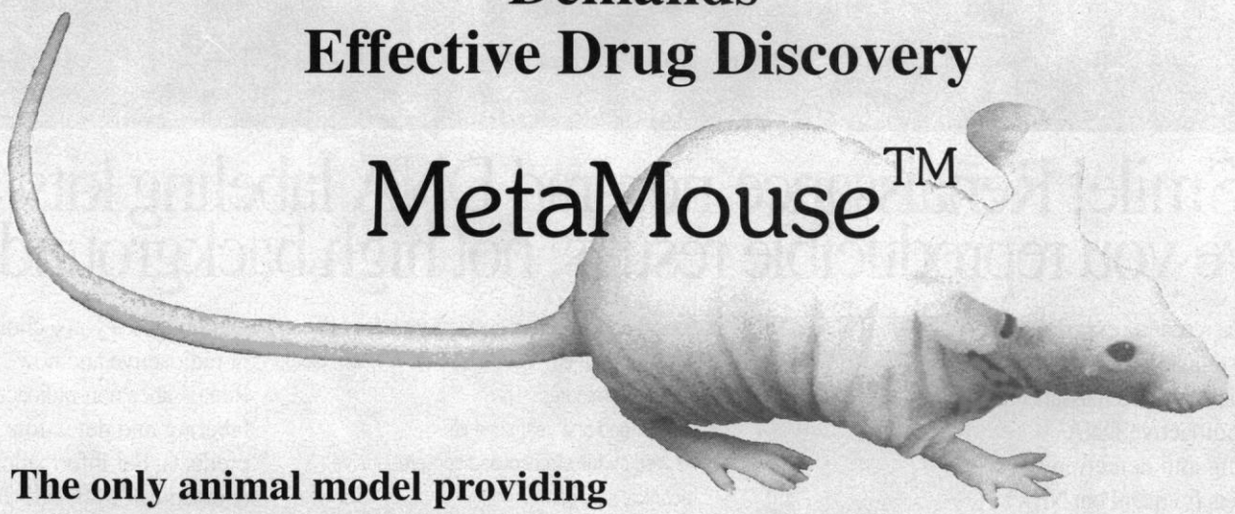

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Basic Research for the Elucidation of

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3. Movement & Behavior
4. Memory & Learning
5. Language & Thinking

(M) Biological Functions through Molecular Level Approaches

1. Expression of Genetic Information
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The program will only support research that **transcends national boundaries**. Thus, **research grants** will be awarded for programs that involve collaboration between teams in different countries; **fellowships** are available to young post-doctoral scientists who wish to work in a different country; and support will be provided for international **workshops**.

RESEARCH GRANTS Grants for basic research *(up to 3 years)* carried out jointly by research teams in different countries. The principal applicant must be from one of the eligible countries*.

FELLOWSHIPS **Long Term** *(1- 2 years)* and **Short-Term** *(up to 3 months)* Fellowships for researchers early in their careers and from the eligible countries* who wish to do post-doctoral research in foreign countries, or for young researchers from outside the eligible countries who wish to do research in one of the eligible countries*.

WORKSHOPS Grants for international workshops organized by researchers from the eligible countries.

*** Current eligible countries are Belgium, Canada, Denmark, France, Germany, Greece, Italy, Japan, Luxembourg, the Netherlands, the Republic of Ireland, Spain, Switzerland, the UK and the USA .**

RESEARCH GRANTS AND LONG-TERM FELLOWSHIPS : APPLICATION DEADLINE IS 1 SEPTEMBER 1994
(awards to be announced in April of the following year)

Applications for **Short-Term Fellowships** and **Workshops** can be submitted **throughout the year**

Guidebooks and application forms will be available in mid-April 1994 and may be obtained upon written request by addressing the form below to the HFSP. Applications using previous year's forms are not accepted.

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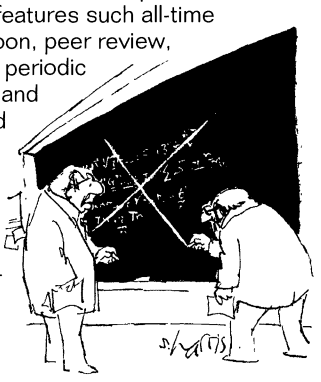

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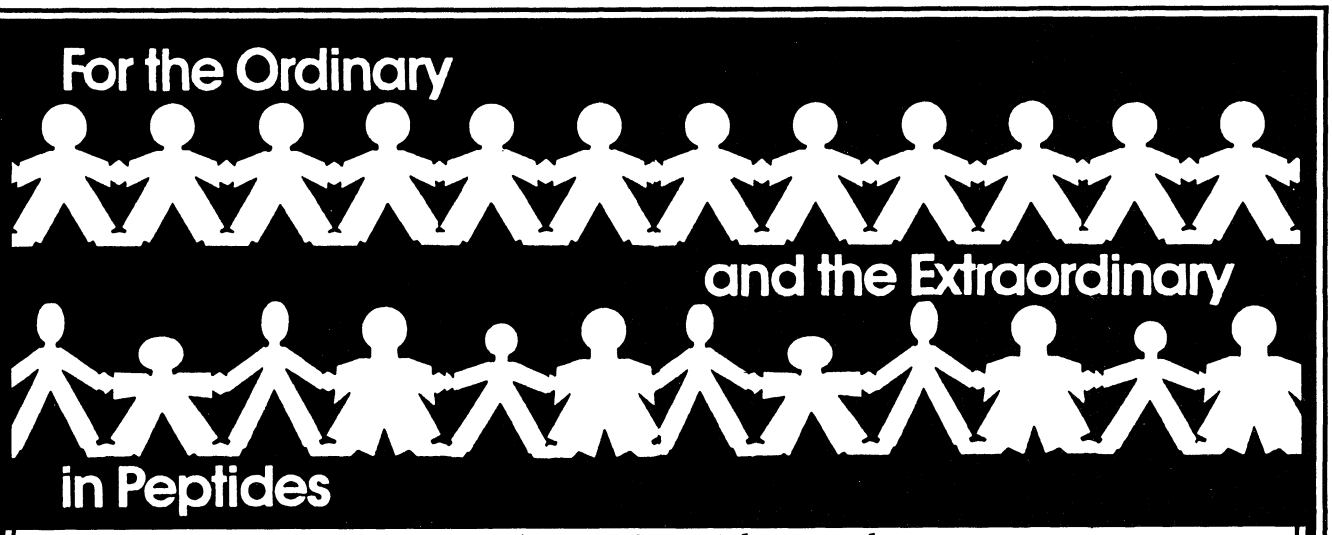

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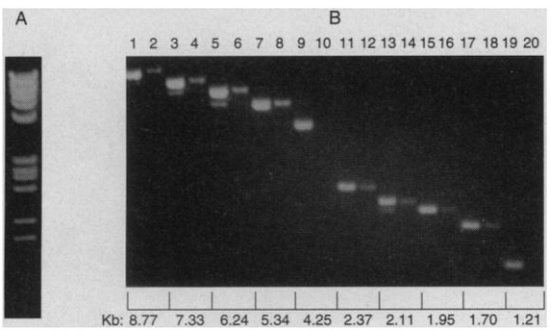
NaI/glass bead kits give about 50% recovery for 2–15 Kb DNA (see figure) and much less outside of that size range.



Recoveries of 1.2 to 8.8 Kb DNA fragments excised from a 1% LMP-agarose gel (Figure A) were consistently much greater using GELase (Figure B, odd numbered lanes) than using a commercial kit containing sodium iodide and silica matrix (Figure B, even numbered lanes).

2. High molecular weight DNA, even megabase DNA, is not damaged using GELase.

DNA larger than 15 Kb is sheared using NaI/glass bead kits.

3. GELase is easy to use.

Just melt the gel slice with GELase Buffer, add GELase and incubate at 45°C to digest. To concentrate the DNA, add ethanol. The gel digestion products are soluble and won't precipitate with the DNA.

4. GELase is inexpensive.

One unit of GELase digests 600 mg of a 1% LMP-agarose gel in 1 hour in GELase Buffer. With a 10-hour incubation instead of 1 hour, the 200-unit size of GELase is enough to digest more than a KILOGRAM of a 1% gel.

5. DNA purified using GELase is ready to use and biologically active.

Some companies recommend two rounds of purification with a NaI/glass bead kit to obtain DNA for cloning. That's not necessary with GELase. DNA recovered using GELase is ready for use in restriction mapping, cloning, labeling, sequencing or other molecular biological experiments.

6. GELase is active in electrophoresis buffers.

It digests gels in TAE, TBE, MOPS and phosphate buffers. Special NaI/glass bead kits are needed for gels in TBE buffer.

7. Protocols for using GELase are the same for RNA as for DNA.

GELase is RNase-free and active in MOPS or phosphate buffers that are used for RNA gels. In contrast, a special version of NaI/glass bead kit is needed for purification of RNA.

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GELase is a novel enzyme preparation that digests the carbohydrate backbone of agarose into small soluble oligosaccharides, yielding a clear liquid that will not become viscous or gel even on cooling in an ice bath. It permits simple and quantitative recovery of intact DNA or RNA from low melting point (LMP) agarose gels. GELase contains no contaminating DNase, RNase or phosphatase.

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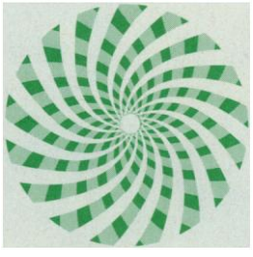

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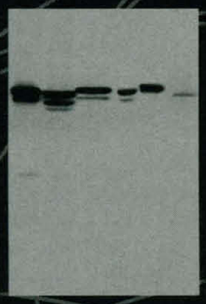
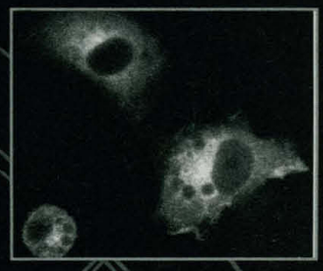


Anti-ISGF3, Western blot.



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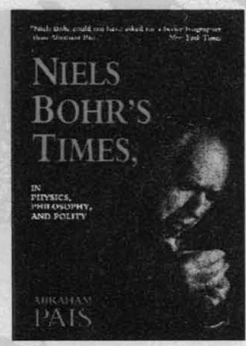

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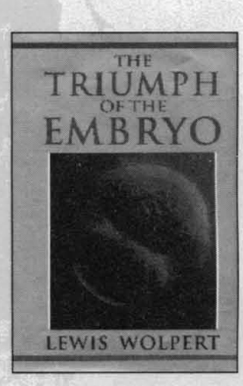

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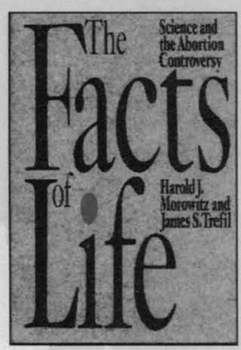

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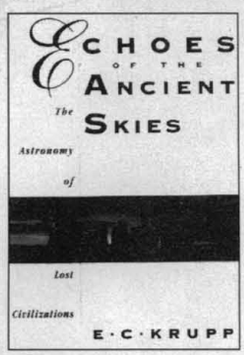

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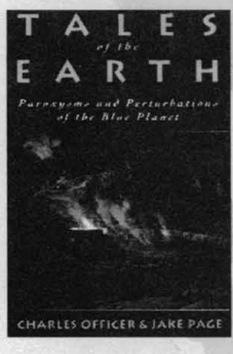

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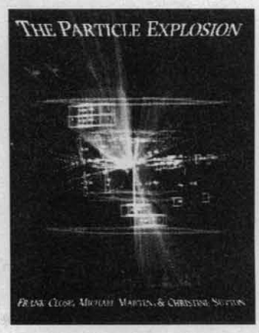

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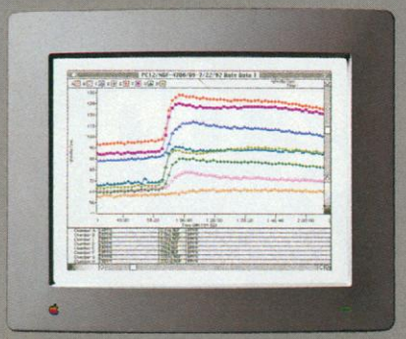
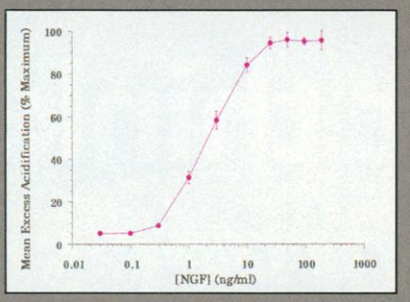
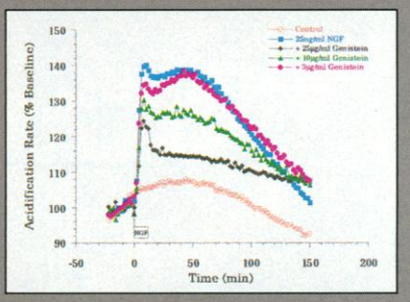
NGF



1 Real-time acidification rate data showing the response of PC12 cells to a 12 min. exposure to nerve growth factor (NGF:0.1-200ng/ml).

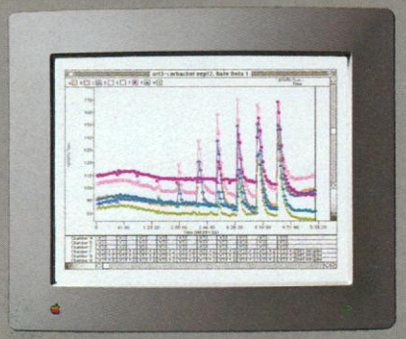


2 Dose response of PC12 cells to NGF. Each point represents data from 7 separate experiments. Calculated EC_{50} value for NGF was 1.9 ± 0.7ng/ml (~152 ± 50pM) ($\bar{x}$ ± S.E.M.).

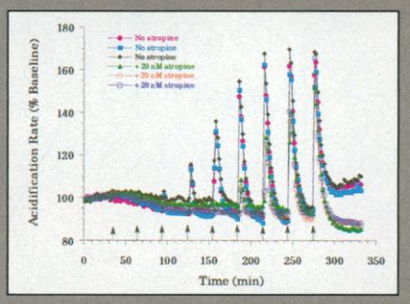


3 Dose dependent inhibition of NGF (25ng/ml) response by tyrosine kinase inhibitor, genistein (3-25μg/ml).

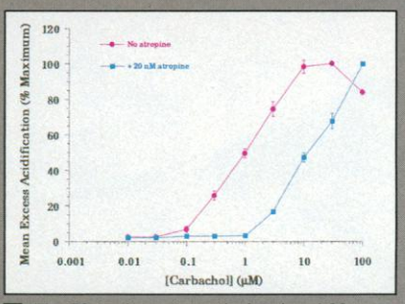
CARBACHOL



1 Real-time acidification rate data demonstrating stimulation of CHO cells transfected with muscarinic M_1 receptor. Increasing doses of carbachol (10nM-100μM) given in presence and absence of 20nM atropine.



2 Data from previous figure expressed as percentages of the basal acidification rates before initial addition of carbachol.



3 The EC_{50} values were calculated as 1.00 ± 0.08μM for carbachol alone and 11.50 ± 0.09μM for carbachol in the presence of 20nM atropine ($\bar{x}$ ± S.E.M.;n = 3).

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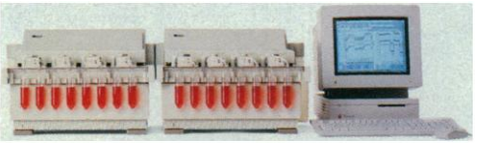

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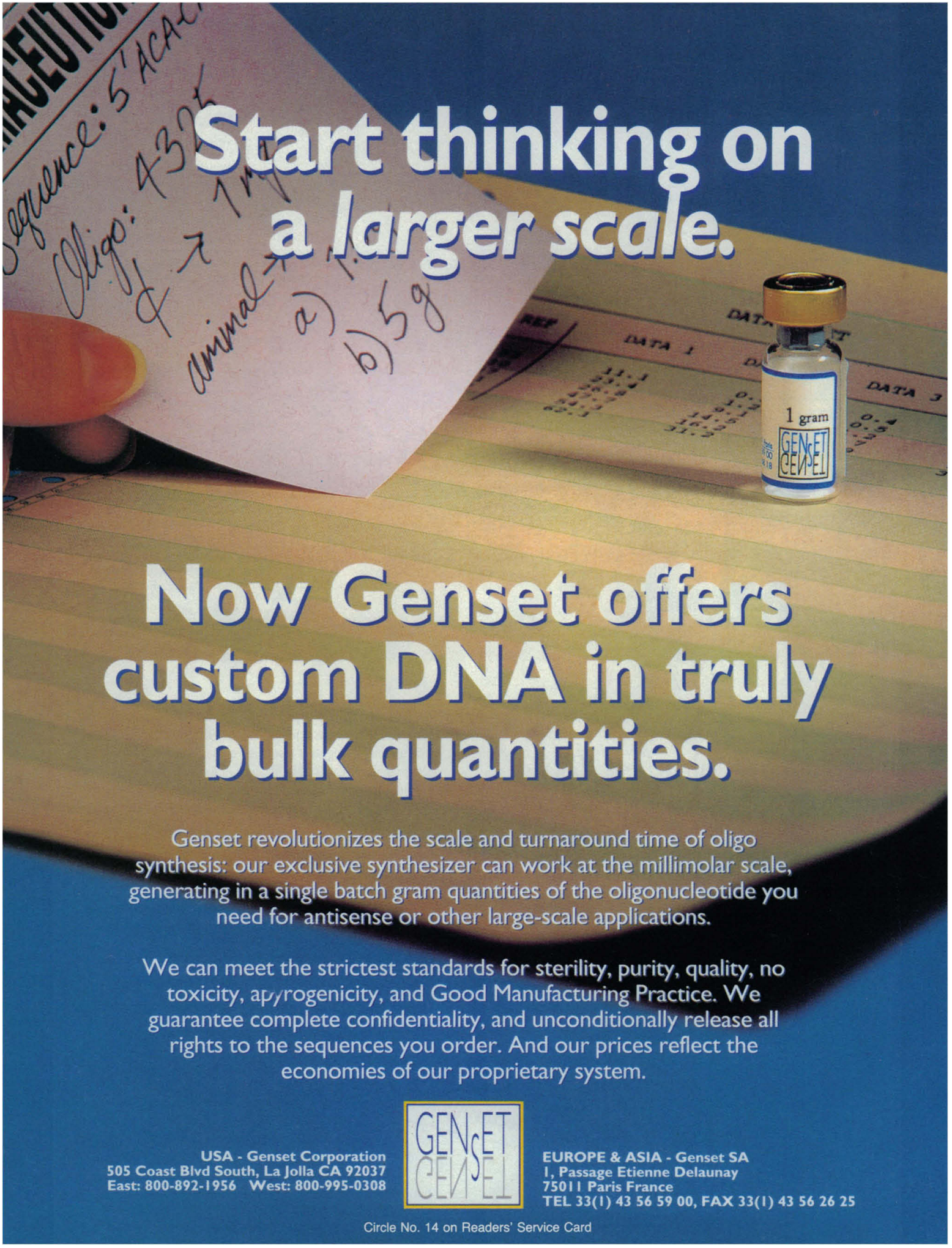
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The Space Station. It's about life on Earth.

PROGRESS REPORT

APRIL 1994

SCIENCE ADVANCES ONE STEP AT A TIME. BUT WITH THE SPACE STATION, IT COULD TAKE A QUANTUM LEAP.

The Space Station will be the largest and most advanced international laboratory ever built for research in space.

So for the first time ever, scientists from around the world will have consistent, long-term access to the unique condition of microgravity.

BASIC RESEARCH THAT COULD BENEFIT MILLIONS OF PEOPLE LIVING TODAY.

More than 600 experiments have already been proposed for the Station. And a number, particularly in the areas of life sciences and materials research, promise significant reward.

The study of human proteins is a good example.

Many diseases are the result of proteins that no longer work as they should. Many others are caused by foreign proteins that enter our bodies through viruses or bacteria.

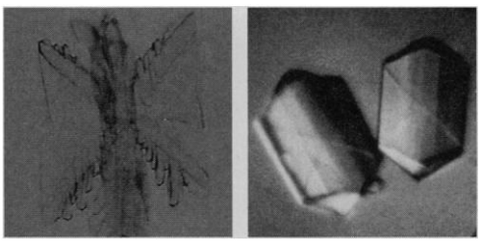
Altogether, we have about 150,000 different proteins in our bodies. But medical researchers only understand the fundamental structures of about 1,200.

If we could define the basic architecture of the proteins we don't understand today—especially enzymes and hormones—we may be able to create drugs that will attach themselves to the proteins, and therefore alter behavior at the molecular level.

In other words, it might be possible to tailor-make drugs for specific proteins that cause cancer, AIDS, diabetes, heart disease, emphysema, arthritis, and dozens of other diseases.

And since each drug would be customized for a disease-causing protein, there's a good chance it would minimize side effects.

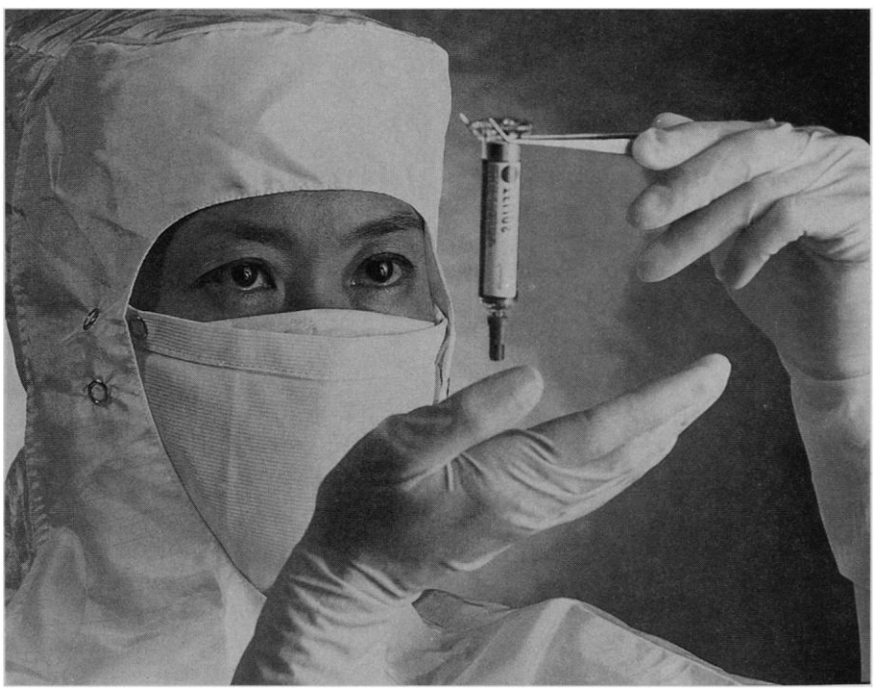
How do we go about studying the basic structures of complicated proteins?



Examples of the same protein crystallized on Earth, left, and in space, right. Ounce for ounce, good protein crystals could be the most valuable items in the world.

One of the techniques used today is called crystallography.

To use this technique, researchers must first isolate the protein in a solution. Then they let the solution solidify over time into a crystal. Once they have a crystal that's large and well-formed, they take multiple X-rays. From the X-ray images, they can then create three-dimensional computer models.



HERE'S WHERE THE SPACE STATION CAN HELP.

The big bottleneck in the whole process is the creation of good crystals.

In the gravity of Earth, substances of different densities separate into layers (sedimentation). And cold, dense liquids are pulled down, forcing warm, less dense liquids to move up (convection).

As a result, protein crystals grown in solutions on Earth are often small, clumped together, or distorted in shape.

In the Space Station, on the other hand, gravity will be only one millionth as strong as it is on Earth. So sedimentation and convection will be negligable, allowing

crystals to form more slowly and much more perfectly.

We've already demonstrated that we can grow protein crystals in space.

Since 1984, approximately 60 different proteins have been crystallized on space shuttle flights. And several of the crystals have been used to determine the structures of the proteins.

As important as those experiments have been, however, they offer only a glimmer of what we can accomplish in the Space Station.

There, we'll be able to grow crystals for months instead of days or weeks. We'll also be able to monitor progress and make changes as we go along.

So chances are, we'll be able to grow protein crystals with the size and purity that medical researchers can only dream about today.

1993 SPACE STATION MILESTONES:
February—President Clinton calls for redesigned Space Station. ***June***—Three options are offered to the President. Option A is selected. Transition to the new configuration and management structure begins. ***August***—Johnson Space Center (JSC), Houston, is named Host Center. Boeing is chosen prime contractor. McDonnell Douglas and Rockwell are named major subcontractors. ***September***—"Alpha" Space Station design is unveiled. ***November***—Potential Russian contributions are detailed in addendum to "Alpha" plan. ***December***—U.S. and Russia sign agreements for joint shuttle/Mir missions. Russia accepts invitation to join international Space Station. ***December***—Systems Requirements Review is held.
MAJOR MILESTONE FOR EARLY 1994:
Systems Design Review. As we went to press, program managers from NASA, the contractors and the international partners were meeting to evaluate the Station's design status. The SDR establishes the technical baseline for the entire program. Elements for review include how the Station will be utilized, operated, and assembled in space. "This is where we move from concepts to hardware implementation," said Randy Brinkly, Space Station Program Manager. "This is by far the most important technical milestone in the program since last year's redesign of the Station. The SDR will lock in the key technical elements of the system, as well as schedule and cost."

"THE U.S. WILL SAVE $2 BILLION . . . [ON] A SPACE STATION THAT IS LARGER AND IN BETTER ORBIT."

—Vice President Al Gore speaking on the benefits of Russian participation in the Space Station.

The U.S., Canada, Japan, and 13 European nations have asked Russia to join the Space Station team as a full partner. Vice President Al Gore met Russian Prime Minister Viktor Chernomydrid in Moscow in late 1993 for the formal agreement.

The new unified Space Station will have significantly greater capability than previous designs. It will house six crew members rather than four. And current estimates project that Russian participation could shave up to $2 billion off the cost

THE SPACE STATION IS MOVING OFF THE COMPUTER SCREEN AND INTO REALITY.

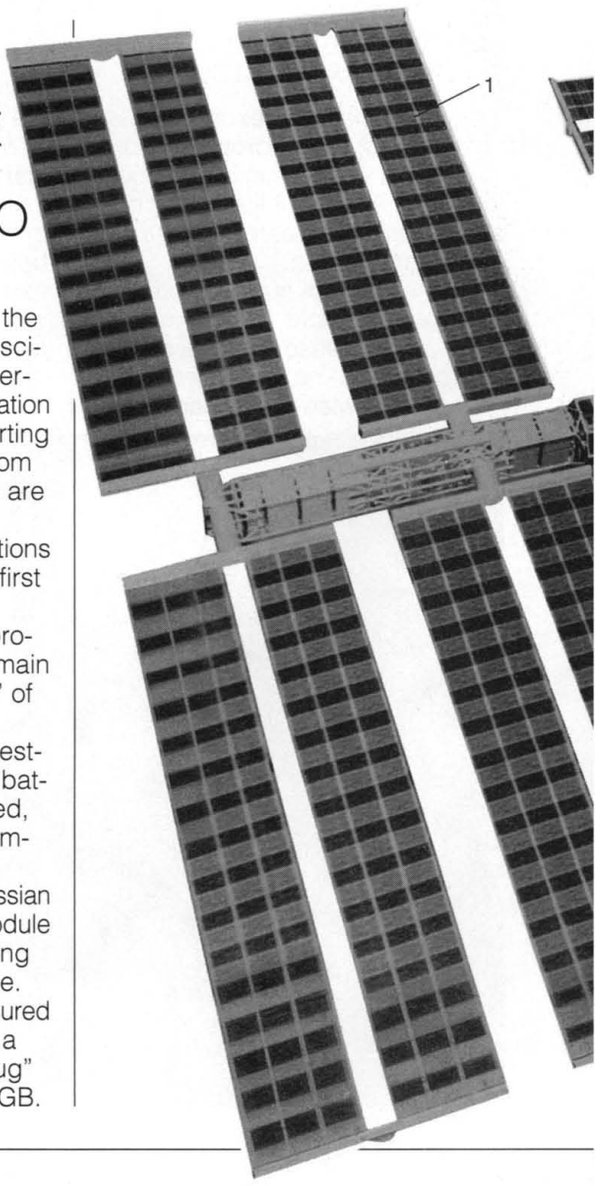
The Space Station will be the largest international venture in science and technology ever undertaken. Modular in design, the Station will be assembled in space starting a little more than three years from now. But many of the elements are already well under way.

Boeing has produced portions of Node 1, the payload for the first U.S. launch.

McDonnell Douglas has produced several sections of the main truss structure, the "backbone" of the Station.

Rockwell is building and testing solar array equipment and batteries, and, along with Lockheed, is delivering solar array test components to Russia.

New to the program are Russian elements including a service module derived from the Mir 2, a docking module, and a research module. The design also involves two assured crew return vehicles based on a Russian Soyuz and a "space tug" based on the Russian Salyut FGB.



for America and allow the Space Station to be finished earlier than previously planned.

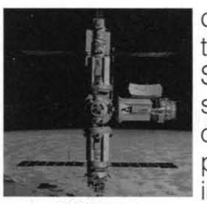
Russia also brings years of space station experience to the U.S.-led international team. Russian orbiting stations have been operating for 22 years. The Mir station, launched in 1986, is still in use. And the performance of the Russian space tug, Salyut FGB, has been extensive and impressive.

THE SPACE STATION WILL BE DEVELOPED IN THREE PHASES.

It will take 34 space flights to complete the Station as now envisioned. 21 of those will be U.S. space shuttle flights and 13 will be Russian launch vehicle flights.

Phase 1

Before assembly starts in space, there will be a series of flights combining astronaut and cosmonaut



PHASE 1

crew activities on the space shuttle, Soyuz, and Mir 1 space station. The object of this phase is to gain in-orbit experience that will greatly reduce the technical risk associated with the assembly and operation of the Space Station. (The first of these flights has already occurred. In early February, a Russian cosmonaut flew aboard the 8-day space shuttle flight STS-60.) Up to 10 flights to the Mir are planned.

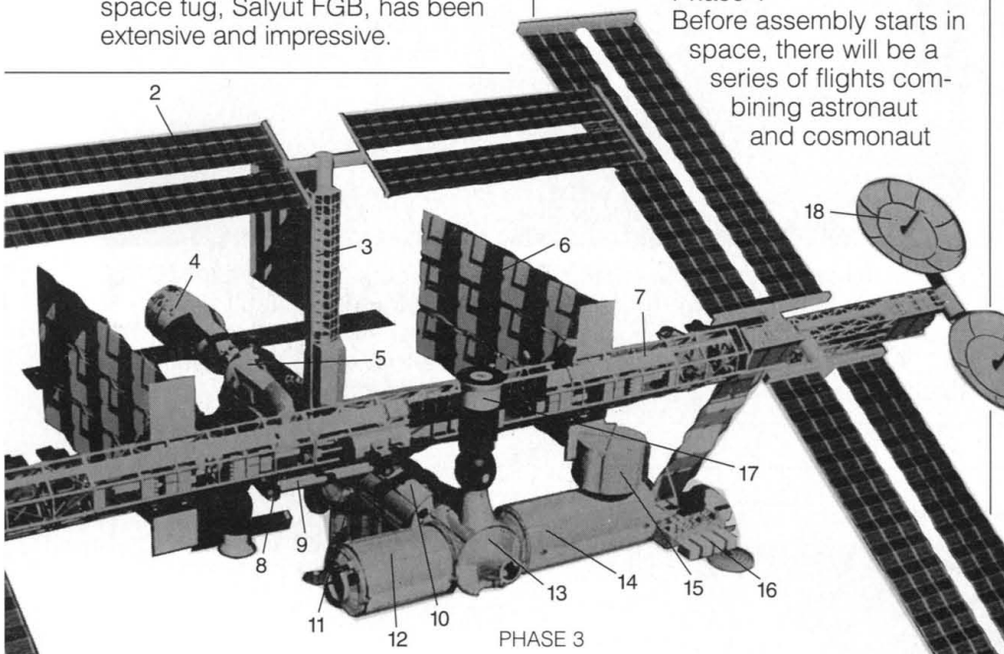
Phase 2

The actual assembly of the Space Station will begin in Phase 2. First element launch is scheduled for December, 1997. Following will be another 10 flights, four by U.S. shuttles and six by Russian launch vehicles. They're all scheduled for 1997-1998. Scientific experiments will begin once the service module is in place (Flight 4). By the end of Phase 2, the "core" of the Station will be complete.

PHASE 2

Phase 3

This final phase will finish construction of the Space Station and will take 17 U.S. and six Russian flights. In Phase 3, the European, Japanese, and Italian modules will be added, as well as final solar array and truss elements. The Station will be completed in October, 2003.



PHASE 3

THE SPACE STATION'S NEW DESIGN

1. Solar Arrays (3)—U.S./Rockwell
2. Solar Arrays (2)—U.S./Russia
3. Power Module—U.S./Russia
4. Mir-derived Service Module—Russia
5. Salyut FGB Space Tug—Russia
6. Thermal Radiators (2)—U.S./McDonnell Douglas
7. Main Truss Structure—U.S./McDonnell Douglas
8. Mini-Pressurized Logistics Module—Italy
9. Mobile Servicing System (Robotic Arm)—Canada
10. Laboratory Module—U.S./Boeing
11. Habitation Module—U.S./Boeing
12. Laboratory Module—European Space Agency
13. Connecting Nodes (2)—U.S./Boeing
14. Experiment Module—Japan
15. Experiment Logistics Module—Japan
16. Exposed Facility—Japan
17. Assured Crew Return Vehicles (2)—Russia
18. Solar Dynamic Power Dishes U.S./Russia

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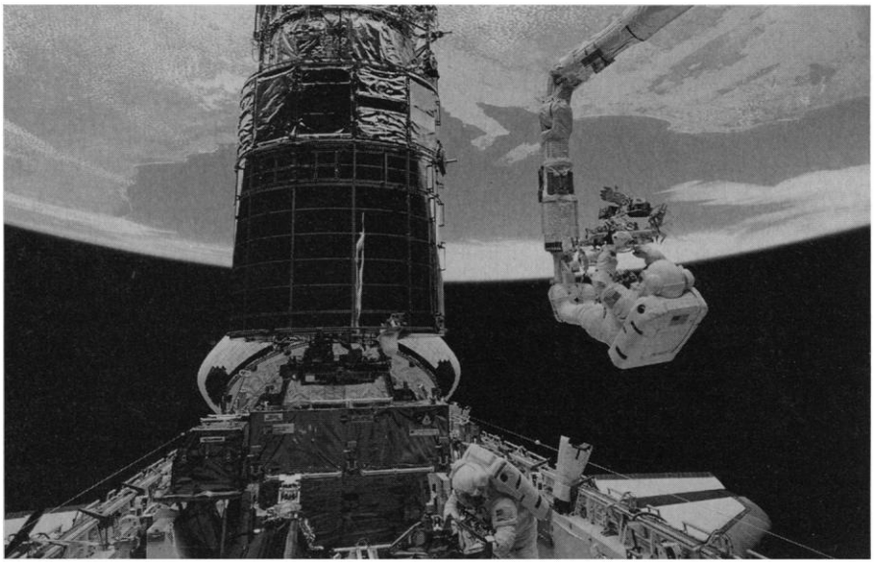
The Space Station. It's about life on Earth.

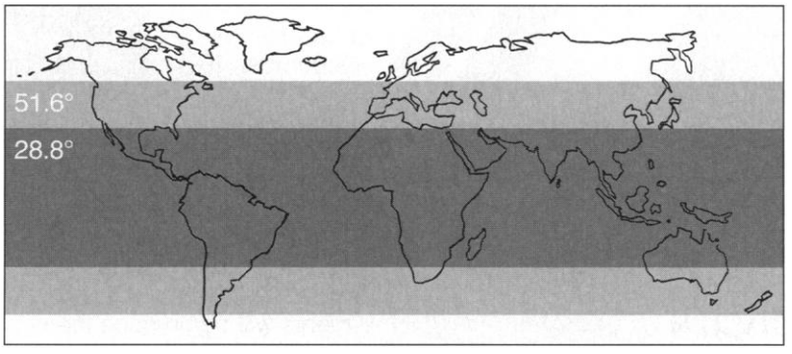
BREATHTAKING HUBBLE SPACEWALKS DEMONSTRATE TECHNIQUES TO BE USED ON SPACE STATION.



When NASA's astronauts walked out into space to repair the Hubble telescope, they not only proved that men and women can handle difficult and physically demanding work in space. They also added momentum to the Space Station program.

Using many of the same tools and techniques that will be utilized in assembling the Space Station, Endeavour's two teams of spacewalkers finished the entire checklist of jobs they were given by NASA.

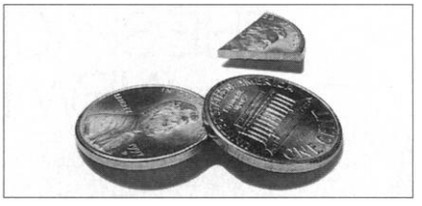
Altogether, they spent a total of 35 hours and 28 minutes working outside the space shuttle. It was the most difficult assignment ever given to a shuttle crew, and the biggest repair job ever done in space.



NEW FLIGHT PATTERN ALLOWS BETTER EARTH VIEW.

The Space Station will fly 248 nautical miles above Earth at 17,500 m.p.h. It will orbit at a 51.6 degree inclination above and below the equator, an orbit that provides a much wider Earth-observation capability than the 28.8 degree inclination planned for earlier designs. This inclination also allows flights to the Station by Russian launch vehicles, something the 28.8 degree inclination did not allow.

THE SPACE STATION COSTS EACH AMERICAN JUST 2.2 CENTS A DAY.



The Census Bureau's January 1 estimate for the U.S. population was 259,353,627 people. And the budget for the United States' portion of the Space Station is $2.1 billion for fiscal year 1994. That works out to 2.2 cents per person per day.

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