Macromolecular Crystallography Utilizing The Microgravity Environment of The Space Shuttle and The International Space Station

Presented to:
Committee on Science
Subcommittee on Space and Aeronautics

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The human body contains approximately 150,000 different proteins that play important roles in the maintenance of life. However, even with today's technology, we lack fundamental knowledge about the structure and mechanism of action for most of these proteins. Crystallography is a tool that can be used to determine the three-dimensional structure of protein and nucleic acids -- information that provides valuable insight into the specific biological roles that these molecules play in our body. Beginning in April, 1985, the U.S. Shuttle has been used for a series of protein crystal growth experiments involving more than 80 co-investigators from pharmaceutical companies, universities, and government facilities*. Higher quality crystals obtained from space have provided new information about proteins implicated in important biological processes as well as diseases such as heart disease/stroke, diabetes, viral hepatitis, bacterial/parasitic infections, influenza, cancer, and emphysema.

Diseases are often caused or influenced by proteins within our bodies that are no longer functioning properly, or by foreign proteins that have entered our bodies (such as those introduced when we are infected by viruses, bacteria, parasites, etc.). Drugs used to help fight various diseases work by binding to the protein that causes the disease. In so doing, the drug alters the biological function of this protein, usually inhibiting its harmful action within our body. In the past, most drugs have been made by trial and error methods, and as a result, they not only affect the protein that is doing harm, but often interact with other proteins within our body producing harmful side effects. Using the three-dimensional structure of the protein involved in a particular disease, drugs can be tailored to interact more effectively with the target protein, but not with other proteins within our body. This reduces unwanted side effects and makes the drug much more useful in the treatment of these diseases.

Today, crystallography is the predominant technique to understand the structure of these complicated proteins. However, to use this technique, the protein must first be crystallized in order to elucidate its structure. The structures of many important and exciting proteins remain a mystery simply because we are unable to obtain crystals of high enough quality or large enough size to use this technique.

When crystals are grown in space, the absence of gravity provides an environment that allows the crystals to grown more perfectly and, in some cases, to much larger sizes than their earth-grown counterparts. In several instances, structures of proteins that could not be determined using earth-grown crystals, despite years of intense effort, could

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* This on-going program is funded by the National Aeronautics and Space Administration. Basic research is performed under the auspices of the Life and Microgravity Sciences and Applications Division (Code UG) and activities associated with commercial development of space are performed as part of a broad program managed by the Space Development and Commercial Research Division (Code UX).

be determined for the first time using the space-grown crystals. Some of the protein crystals produced in space that were superior to anything produced on earth include:

- **Gamma-interferon**, which is important in anti-viral research and for treatment of certain types of cancer
- **Alpha-interferon,** used against chronic hepatitis B and C, hairy cell leukemia, Karposi's sarcoma, multiple myeloma, and melanoma
- **Factor D**, a protein important in heart disease, stroke and complications associated with cardiovascular surgery
- **Insulin,** a protein important in, and used as, a drug for diabetes
- **Elastase**, a key protein known to cause the destruction of lung tissue in patients suffering from emphysema
- **Malic enzyme**, a protein important in the development of antiparasitic drugs
- **Isocitrate lyase**, a protein important for the development of anti-fungal agents
- **Human serum albumin**, the most abundant protein in our blood, responsible for the distribution of many different drugs (even aspirin) to various tissues in our body
- **Canavalin**, a protein isolated from edible plants -- its structure is of interest because the information can be used to genetically engineer more nutritious plants.
- **Proline isomerase**, a protein important in tissue rejection
- **Satellite tobacco mosaic virus** -- even crystals of complete viruses that are of much higher quality and larger size have been obtained from the space experiments. Knowledge of the structure will aid in the development of more effective chemicals to block the harmful actions of viruses on plants.

Space-grown crystals have provided crucial data for drug design. Some examples of success stories follow:

- **Factor D**: Factor D is a plasma protein, a part of the alternate pathway for the human complement system, that is an important structure-based drug design target for reduction of complications from open heart surgery, heart attacks, and strokes. The crystals of Factor D, grown on STS 50, USML-1, were used to determine the protein's three-dimensional structure for the first time. This structure was used to design an inhibitor of the protein's activity; this inhibitor, (a potential drug) is expected to enter human clinical trials this year.
- **Neuraminidase**: Neuraminidase is a protein that occurs on the surface of all strains of the influenza virus and is necessary for viral multiplication. This particular protein is the same in the different strains and, as such, is a prime drug design target for prevention and treatment of the flu. Although the structure of neuraminidase was solved with earth-grown crystals, space-grown crystals have been used to optimize the design of the inhibitor, (the drug). Pharmacology and preclinical studies are ongoing and human clinical trials are anticipated in 1997.
- **Recombinant human insulin**: Recombinant human insulin is the protein pharmaceutical used by patients to delay and mitigate the ravages of diabetes. On

STS 57 and STS 60 our Center flew this protein in collaboration with the Hauptman Woodard Medical Research Institute and Eli Lilly with the objective being structure determination and development of a longer acting insulin formulation. The space-grown insulin crystals provided data that was used to determine the best three-dimensional picture of this molecule to date. This highest resolution structure ever produced revealed details to 1.4Å, a 0.5Å improvement over the best ground data.

Although valuable new information was obtained from these initial experiments, additional high quality crystals are needed to elucidate the final structures for these proteins. Also, a constant supply of crystals is necessary for the drug design phase for those proteins associated with various diseases. The experimental results gathered to date clearly indicate the need for continual, constant and long-term access to this unique microgravity environment. Experiments performed on the shuttle have been exciting and should definitely be continued, but to see rapid and more extensive progress, the International Space Station is needed. Some of the justifications for this are as follows:

- More than 40% of proteins crystallized on earth require more than three weeks for the crystallization process to be completed with crystallization times for some extending as long as three months.
- It is believed that re-entry g-levels from the space shuttle may have harmed several of the crystals grown on previous space shuttle missions. An X-ray Crystallography Facility (XCF) is currently in a Phase B development program that includes requirements definition and prototype development for the International Space Station. This facility will make it possible to collect data from the crystals grown in orbit thereby eliminating the need to return them to Earth, which would subject them to harmful re-entry g-levels.
- The International Space Station will allow experiments to be conducted on a continual basis, 365 days per year. A constant supply of high quality crystals is needed for a period lasting anywhere from two to five years for each protein. The International Space Station will allow crystals to be grown continually, data collected on those crystals, and then transmit the data back to earth for structure determination, and ultimately, for the drug design stages of each project.
- The International Space Station will simultaneously accommodate several thousand different crystallization conditions for as many as 100 scientific laboratories around the world.
- One of the other applications of the XCF technologies that are being considered for inclusion in the station facility is to measure effects of reduced gravity on bone and tissue structures (relating to long-term space travel). Another example is applying x-ray techniques to characterize thin epitaxial films of microelectronic materials.

In summary, it has been demonstrated that protein crystals of superior size and quality can be produced in space and that exhibited differences have contributed directly

to the determination of protein structures, some of which were previously indeterminable. However, the key to seeing rapid progress in this area lies in the ability to use this technique on an extended basis. These results and supportable conclusions more than justify the continuation of the Protein Crystal Growth program using the enhanced conditions represented by the space shuttle and, more importantly, by the complete laboratory facility envisioned for the International Space Station.

Our Center has placed a high priority on fully utilizing the International Space Station environment and resources. We have two concerns, however. The first is the impact of a potential space-access hiatus during the station building phase. Several of our industry partners provided testimony at the Commercial Space Processing and Requirements Forum, March 1996, National Academy of Public Administration. They emphasized that the dearth of flight opportunities would slow their protein crystal growth and structure-based drug design programs. Lack of access will diminish their interest in the space program (by putting it on hold) and the level of their in-house and in-kind investment to NASA's microgravity protein crystal growth program. We believe that it is essential to maintain scientific and drug development progress throughout the station building phase in order to ensure adequate and competitive occupancy for station once its assembly is completed. It is crucial that we maintain a pipeline of activity to feed the capability that the new facility will provide. This is especially true for the structure-based drug design projects currently underway with our industrial partners. We must continue the R/D in order to expedite the flow of tangible benefits (i.e., medicines) into our society.

The second concern, bartering of facilities to offset International Space Station costs, must also be carefully scrutinized. Care must be given to the task assignment process to ensure that United State jobs and competitiveness are not jeopardized.

Background Information

The detailed information that can be learned from the three-dimensional structure of a protein is extremely useful in several ways. From the basic biomedical viewpoint, this information plays a critical role in our understanding of the way that enzymes, receptors, hormones, etc., function in biological systems. Within the pharmaceutical industry, protein structure information can be used to tailor make compounds (drugs) that selectively bind to target sites, and thereby inhibit the activity of the protein. For example, if a particular enzyme is required for the function of a target cell, the cell may be inhibited by designing a drug that "fits" the active site of the enzyme and blocks its activity.

Most of the drugs that are now available have been made by tedious trial-and-error methods. Hundreds of thousands of potential drugs are synthesized and tested in efforts to obtain inhibitors of key proteins within target cells. A more logical approach, which is the foundation of structure-based design, is to obtain the complete three-dimensional structure of a target protein using the techniques of crystallography, and to then specifically design drugs that have the proper shape and distribution of atoms to bind tightly within key sites of the protein and thereby block its biological action. If scientists could determine the three-dimensional structure of the protein involved in a particular disease, they could use that structure information to tailor-make drugs that more effectively interact with the protein that is causing harm, and minimize the drug's effects on other proteins within our body. This would reduce unwanted side effects and make the drugs much more effective in the treatment of various diseases.

A second highly promising commercial application of protein crystallography is the area of protein engineering. Current techniques of molecular biology permit investigators to specifically alter protein molecules through site-directed mutagenesis, which is a technique for modifying the DNA molecules that code for the protein. Although the techniques involved in protein engineering are under intense development at this stage, it is generally accepted that these methods will prove to be of tremendous practical value for the design of entirely new types of enzymes that can be used as catalysts for mediating a variety of reactions, and for the design of biological modulators and other pharmaceutical agents that have carefully engineered physical and biological properties. As a general rule, the most promising approaches to protein engineeringrely upon detailed structural information about the proteins of interest. At the present time, this sort of information can only be obtained by the technique of protein crystallography.

Today, x-ray crystallography is the only technique that allows scientists to see complicated structures at the atomic level. However, to use this technique, scientists first must crystallize the protein whose structure they want determined. The crystallization step is the major bottleneck that prevents crystallography from being used as a tool to help scientists better understand the mechanism of action of thousands of proteins within

our body and for those proteins involved in disease processes to use their structure to synthesize pharmaceutical compounds. For this reason, our laboratory, in conjunction with more than 80 co-investigators from 32 universities and 22 companies from around the world, have been involved in: (1) intensive ground-based investigations designed to elucidate the basic mechanisms involved in crystal growth processes and (2) in space experiments designed to explore the possible benefits of using a microgravity environment for protein crystal growth.

Beginning in April 1985, protein crystal growth experiments have been conducted on 32 different space shuttle flights using many different variations of hardware and crystallization techniques. The results from these experiments have conclusively shown that the microgravity-grown crystals are often larger, display more uniform morphologies, and yield significantly better data than the best crystals of these proteins ever produced on earth. In every case, crystals of the proteins grown in space are compared with the very best crystals ever produced on earth regardless of the crystallization method or the length of time it took to produce those crystals on earth. (In many instances, these projects have been worked on for several years by universities and pharmaceutical companies with thousands of experiments performed on earth.) In spite of this unfair comparison, the microgravity-grown crystals have proven to be significantly better in a number of cases.

Combined with the significant accomplishments from microgravity crystal growth, NASA has committed significant funds toward studies designed to provide better understanding of crystal growth processes. This research has led to the discovery of new crystallization techniques used on earth that have provided significant enhancements in quality for earth-grown crystals for several investigators in this country. In addition, these ground-based initiatives have led to alternative crystallization techniques specifically developed to take advantage of a microgravity environment. One such technique was used in new hardware developed for microgravity experiments and has flown on 12 recent shuttle flights. The results from these flights were exciting; a 75% success rate was experienced as judged by crystal size and quality for the four proteins that were tested. Future hardware currently under development for microgravity experiments will allow astronauts to optimize the crystal growth conditions for long duration shuttle flights and for the International Space Station.

It is difficult to predict when a useful drug will result from protein crystal growth in space. One must realize that the development of pharmaceutical compounds typically takes anywhere from 6 to 20 years from the initial basic research stages all the way through the required human clinical trials needed for FDA approval. What must be realized is that in some cases without crystals of high enough quality it may never become possible to determine the three-dimensional structures for proteins involved in various diseases. In the past, this has seriously impeded efforts to produce useful drugs. It is clear from the 32 microgravity protein crystal growth experiments performed on the

United States Space Shuttle that crystals of superior quality and/or size can be produced in space. In several cases, the differences were significant in that they transformed projects that, after years of intense effort had seen little or no progress on earth into ones that now, for the first time, would allow complete structures to be determined. The higher quality crystals obtained from space can reduce the time required to develop useful drugs for many different diseases and may allow drugs to be developed that would have been extremely difficult to design, if at all, without use of space crystals.

Companies, universities, and government facilities affiliated with this NASA-sponsored project:

Companies

Company	Location
• Atlantic BioPharmaceuticals, Incorporated	Idyllwild, California
• BioCryst Pharmaceuticals	Birmingham, Alabama
• Boeing Defense Group	Huntsville, Alabama
• Brazsat	Brazil
• Bristol-Myers Squibb	Princeton, New Jersey
• Cubist Pharmaceuticals	Cambridge, Massachusetts
• DigiCon	Brazil
• Diversified Scientific, Inc.	Birmingham, Alabama
• DuPont Merck Pharmaceutical Co.	Wilmington, Delaware
• Eli Lilly Company	Indianapolis, Indiana
• Ibbex, Inc.	Birmingham, Alabama
• Molecular Structure Corporation	The Woodlands, Texas
• Parke-Davis	Ann Arbor, Michigan
• Pasteur Merieux Connaught Pharmaceutical Co.	Swiftwater, Pennsylvania
• Schering-Plough Research Institute	Kenilworth, New Jersey
• SmithKline Beecham Pharmaceuticals	King of Prussia, Pennsylvania
• Space Industries, Incorporated	League City, Texas
• SpaceHab, Inc.	Washington, D.C.
• Sterling Winthrop	Collegeville, Pennsylvania
• The Upjohn Company	Kalamazoo, Michigan
• Uniao Quimica	Brazil
• Vertex Pharmaceuticals	Cambridge, Massachusetts

Universities

University	Location
• Australian National University	Acton, Australia
• Catholic University of the North	Chile
• CENG	Grenoble, France
• E.A.R.T.H.	San Jose, Costa Rica
• EMBL	Hamburg, Germany

• Georgia Institute of Technology	Atlanta, Georgia
• Hauptman-Woodward Research Institute	Buffalo, New York
• Hospital for Sick Children	Toronto, Ontario, Canada
• Kyoto University	Kyoto, Japan
• McMaster University	Hamilton, Ontario, Canada
• Mississippi State University	Starkville, Mississippi
• Ohio State University	Columbus, Ohio
• Pennsylvania State University	State College, Pennsylvania
• Rutgers University	Piscataway, New Jersey
• Texas A&M University	College Station, Texas
• University of Alabama in Huntsville	Huntsville, Alabama
• University of California, Riverside	Riverside, California
• University of Connecticut	Storrs, Connecticut
• University of Georgia	Athens, Georgia
• University of Groningen	Groningen, Netherlands
• University of Houston	Houston, Texas
• University of Milan	Milan, Italy
• University of Minnesota	Minneapolis, Minnesota
• University of North Carolina, Chapel Hill	Chapel Hill, North Carolina
• University of Pennsylvania	Philadelphia, Pennsylvania
• University of Sao Paulo	Brazil
• University of Santiago	Santiago,Chile
• University of Saskatchewan	Saskatoon, Saskatchewan, Canada
• University of Texas, Galveston	Galveston, Texas
• University of Washington	Seattle, Washington
• University of York	York, England
• Vanderbilt University	Nashville, Tennessee
• Yale University	New Haven, Connecticut

Government Facilities

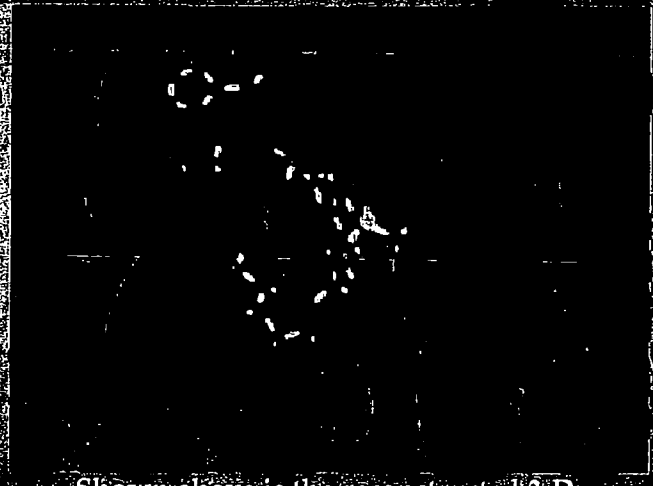
Facility	Location
• Brookhaven National Laboratory	Upton, New York
• Marshall Space Flight Center	Huntsville, Alabama
• National Research Council of Canada	Ottawa, Ontario, Canada
• U.S. Naval Research Laboratory	Washington, DC
• Lewis Research Center	Cleveland, Ohio

Space Research and Heart Surgery

Open heart surgery offers hope for a new lease on life, but the trauma caused by the surgery itself often triggers massive inflammation. This is because the immune system, which fights external factors, overreacts. Factor D is the protein which plays a key role in the biological steps that activate this immune response.

By blocking the natural action of Factor D, the immune system is prevented from inappropriately running "out of control," allowing the patient to recover more rapidly.

To know how to block this protein, detailed data about its 3-D structure is needed.



Shown above is the reconstructed 3-D structure of Factor D determined from crystals grown in space.

Factor D crystals grown in space were used to determine this 3-D structure.

This data from crystals grown in space allowed researchers to develop inhibitors which specifically block Factor D's active site.

Factor D blockers, with their great potential to alleviate the complication of inflammation associated with heart surgery, are now being developed for clinical trials. This work is being spearheaded by The Center for Macromolecular Crystallography together with its corporate partner. These new drugs, developed from space research, should be commercially available as soon as 2001!

DIABETES RESEARCH AND TECHNOLOGY

What is the Scope and Impact of Diabetes?

- Affects 16 million people
- A leading cause of death and disability
- Costs $92 billion per year.

Who Gets Diabetes?

- People of any age

There is research being pursued by NASA that can have an impact on the fight against diabetes. These efforts are making use of NASA-developed technology and are being pursued cooperatively with outside partners.

NASA Protein Crystal Growth: A particularly important result from the NASA flight research was obtained on recombinant human insulin. On two shuttle missions, Dr. G. David Smith of the Hauptman-Woodward Medical Research Institute, flew human insulin complexed with a drug that improves the therapeutic effect of insulin. The space grown crystals allowed Dr. Smith to obtain a large refinement of the structure, which provided first time understanding how this compound binds in the insulin crystal and affects the therapeutic time-release properties. Researchers are currently working on designing nontoxic drugs that will bind to the insulin and allow its use in diabetic patients. This was made possible by the information obtained from space grown crystals.

NASA Fiber Optic Probe Technology for Detection of Cataracts and Diabetic Retinopathy: The NASA probe was originally developed for space experiments onboard the Space Shuttle and is now being applied to study eye diseases in collaboration with NEI/NIH (Inter-Agency Agreement, 10/96) and FDA (Inter-Agency Agreement being developed). These studies are focused on noninvasive early diagnosis of cataracts and diabetic retinopathy. Diabetic retinopathy is the fourth leading cause of all legal blindness. Diabetic retinopathy and cataracts can be detected at their early stages using NASA's fiber optic probe technology. The capability of diagnosing disease in its earliest stage, in a noninvasive and quantitative fashion, holds promise for patient treatment before surgery becomes necessary.

Culture of Human Islet Cells: A biopharmaceutical company is using NASA-developed bioreactor technology to culture human insulin-secreting pancreas cells for treatment of diabetes. This approach could replace insulin therapy by introducing functional insulin-secreting pancreatic tissue into patients with insulin-dependent diabetes. The pancreatic tissue is protected from attack from the patient's immune system by inert encapsulation. The NASA bioreactor may be critical to providing a source of functional human pancreatic tissue.

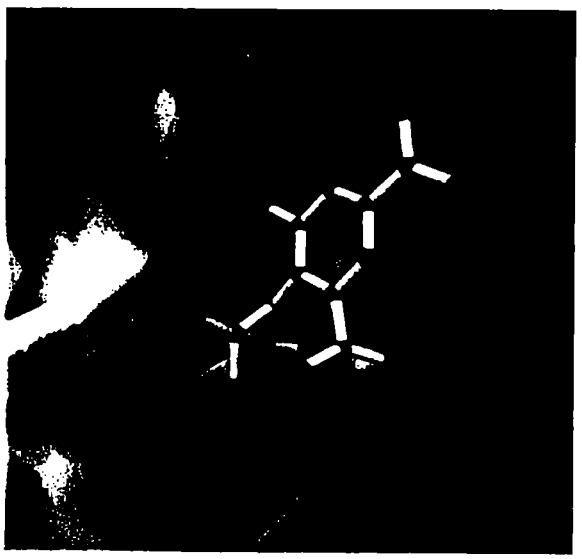
Flu Treatment from Commercial Space Research

As many different strains of influenza as there are, they all have something in common, their reproduction processes are dependent on the same enzyme -- neuraminidase. Pharmaceutical companies have been developing drugs which target this neuraminidase enzyme. A drug that can inhibit the function of neuraminidase would prove an effective weapon against the flu.

Scientists from the pharmaceutical industry have turned to space in their development of a neuraminidase-inhibiting drug. Partnered with researchers from the Center for Macromolecular Crystallography, a NASA Commercial Space Center, scientists have grown crystals of neuraminidase on the STS-73 Space Shuttle flight.

The Center for Macromolecular Crystallography is one of nine NASA Commercial Space Centers whose objective is to facilitate the use of space for commercial products and services.

Drugs inhibit the neuraminidase by attaching themselves to the enzyme. The improved, space-grown neuraminidase crystals have provided information that helped design drugs to form a stronger interaction with the enzyme. Since the drugs are less likely to detach from the enzyme, they are more effective, require smaller dosages, and have fewer side effects.



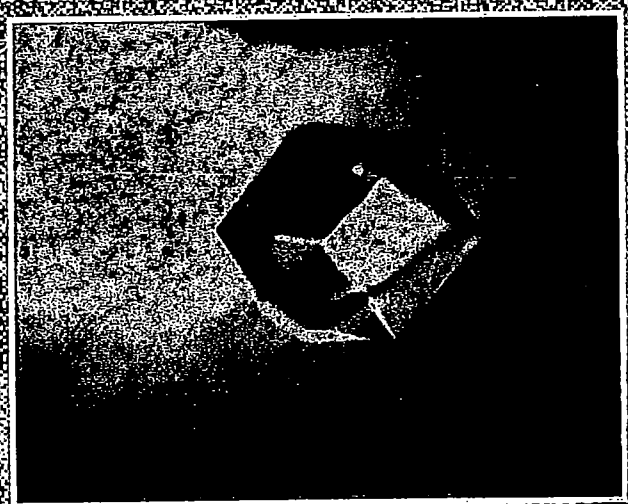
Illustrated here is a segmented representation of the inhibitor compound sitting inside a cave-like contour of the neuraminidase enzyme surface. This cave-like formation present in every neuraminidase enzyme is the active site crucial to the flu's ability to infect. The space-grown crystals of neuraminidase have provided significant new details about the three-dimensional characteristics of this active site thus allowing researchers to design drugs that fit tighter into the site.

The CMC holds one patent for a neuraminidase inhibitor. Clinical trials involving human subjects are anticipated this year. The success envisioned in the clinical trials is expected to lead to a marketable treatment for the flu.

For more information about this and other activities of the Commercial Space Centers, contact Ed Gabris at (202) 358-4495 or at egabris@hq.nasa.gov or Rose Allen at (205) 544-0117 or Rosalie.W.Allen@msfc.nasa.gov.

New anti-parasite drug?

Over a billion of mostly third world people are infected with a roundworm known as ascarids. Ascarids are tiny parasites that infect the intestinal tract of vertebrates. Movement of the larvae into the brain or other parts of the body can prove fatal. Space-based research is providing new hope in combating these parasitic worms. Ascarids are dependent upon a substance known as malic enzyme to regulate certain bodily functions. A new drug designed to interfere with normal functioning of malic enzyme should prove deadly to ascarids.



For over two years, UpJohn had been stymied in its efforts to produce malic enzyme crystals of the quality needed to determine its structure for drug design. The Center for Macromolecular Crystallography, along with the University of North Texas have since grown malic enzyme crystals on the USML-1 Spacelab mission. Although these crystals proved to be smaller than ground based ones, they were more perfectly formed, therefore producing better data for drug design.

Flu remedy coming soon from research in Space

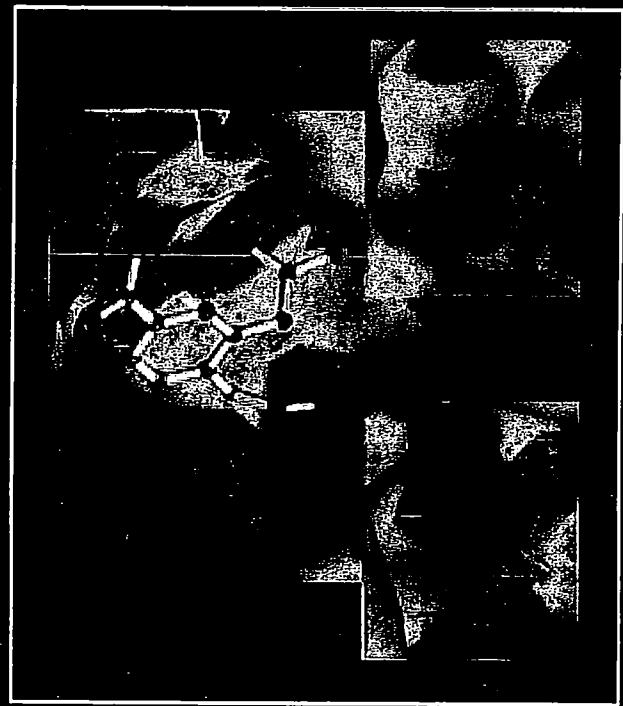
Influenza affects 20 to 40 million people and results in some 20 thousand deaths annually in the US, but relief is on the way!

The loss of productivity due to flu is staggering. Costs range as much as $20 billion/year.

High mutation rates of the flu virus have hindered development of new drugs or vaccines.

But new data from *protein crystals grown in space and on earth* have unlocked the secret of the flu bug and revealed its Achilles heel!

The secret lies in a small molecule which is attached to the host cell's surface. Each flu virus, no matter what strain, must remove this small molecule to escape the host cell to spread infection.



Three Dimensional Protein Structure reconstructed from x-ray crystallography image.

Using data from space and earth grown crystals, researchers from the Center of Macromolecular Crystallography (CMC) are designeing drugs (*keys*) to bind with this protein's active site (lock).

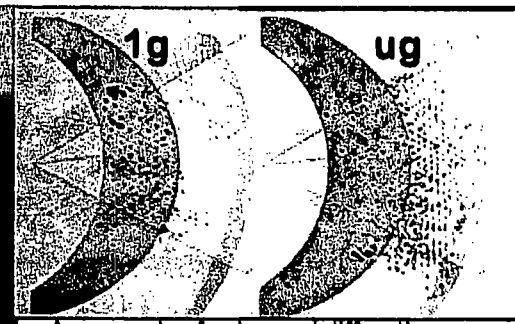
This lock and key fit reduces the spread of flu in the body by blocking its escape route.

In collaboration with its corporate partner, the CMC has refined drug structure in preparation for clinical trials.

Tested and approved relief is expected to reach drugstores by 2004.

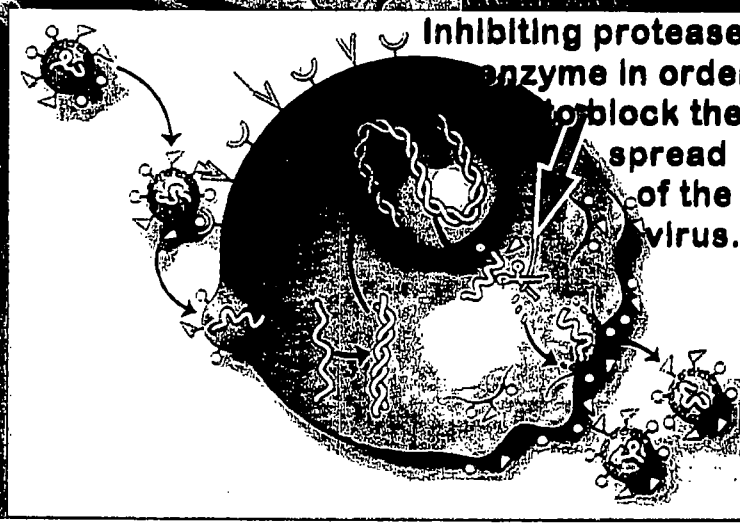
NASA

...nst Aids



An example of enhanced diffraction data from space grown crystals

3- drug cocktails are currently the most promising therapy in the fight against AIDS.

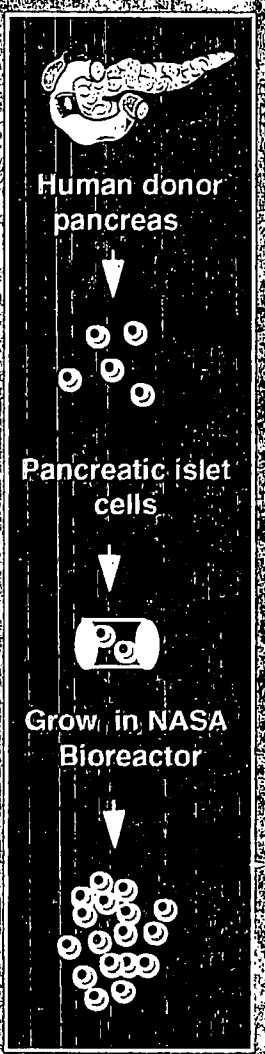


Inhibiting protease ...nzyme in order ...o block the spread of the ...virus.

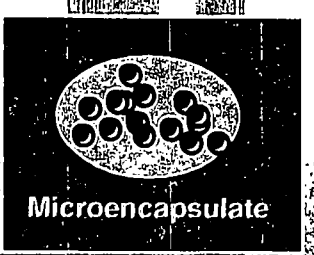
Space Research and Diabetes

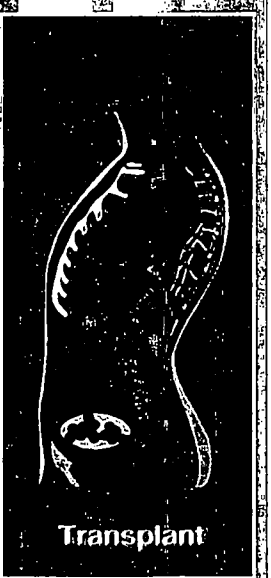
Diabetes is the 3rd leading cause of death in the U.S. It is also the leading cause of complications such as blindness and lower limb amputations, at a cost of $100 billion per year!

The NASA Bioreactor--a device which allows us to grow tissue outside of the human body--may play a crucial role in a promising new treatment for diabetes!



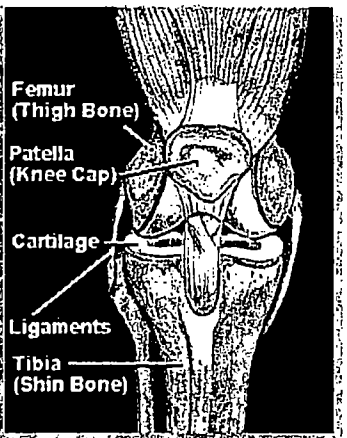
Forthcoming experiments plan to grow human pancreatic islet cells in the Bioreactor for possible microencapsulation and transplantion into diabetic patients. Thus far, clinical trials using this technique with porcine islet cells are very promising. Transplanted pancreas tissue produces insulin, reducing the need for insulin injections and minimizing complications such as blindness and limb loss.





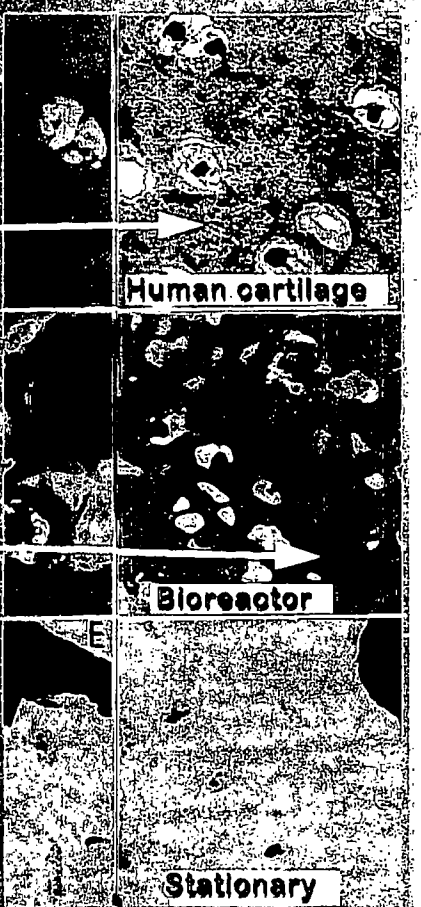
The Bioreactor has the potential for changing disease treatment in our society through tissue transplants. A commercial entity is planning to use the NASA Bioreactor to grow pancreatic tissue for possible use in the treatment of diabetes.

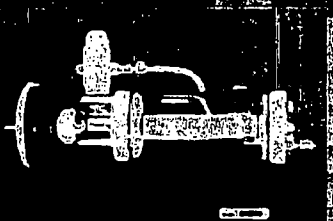
Space research & tissue transplant



Cartilage is the crucial material in bone joints. Its deterioration leads to debilitating conditions, including arthritis. Understanding cartilage development is important in both the prevention and treatment of joint injuries.

Compared to traditional stationary cultures, the Bioreactor grown tissue produces matrix material which closely resembles cartilage found in the human body (right). It is this matrix material which gives cartilage its mechanical strength. This may give researchers not only new insight into chronic joint deterioration, but also open up the possibility of growing cartilage tissue for replacement and transplantation.

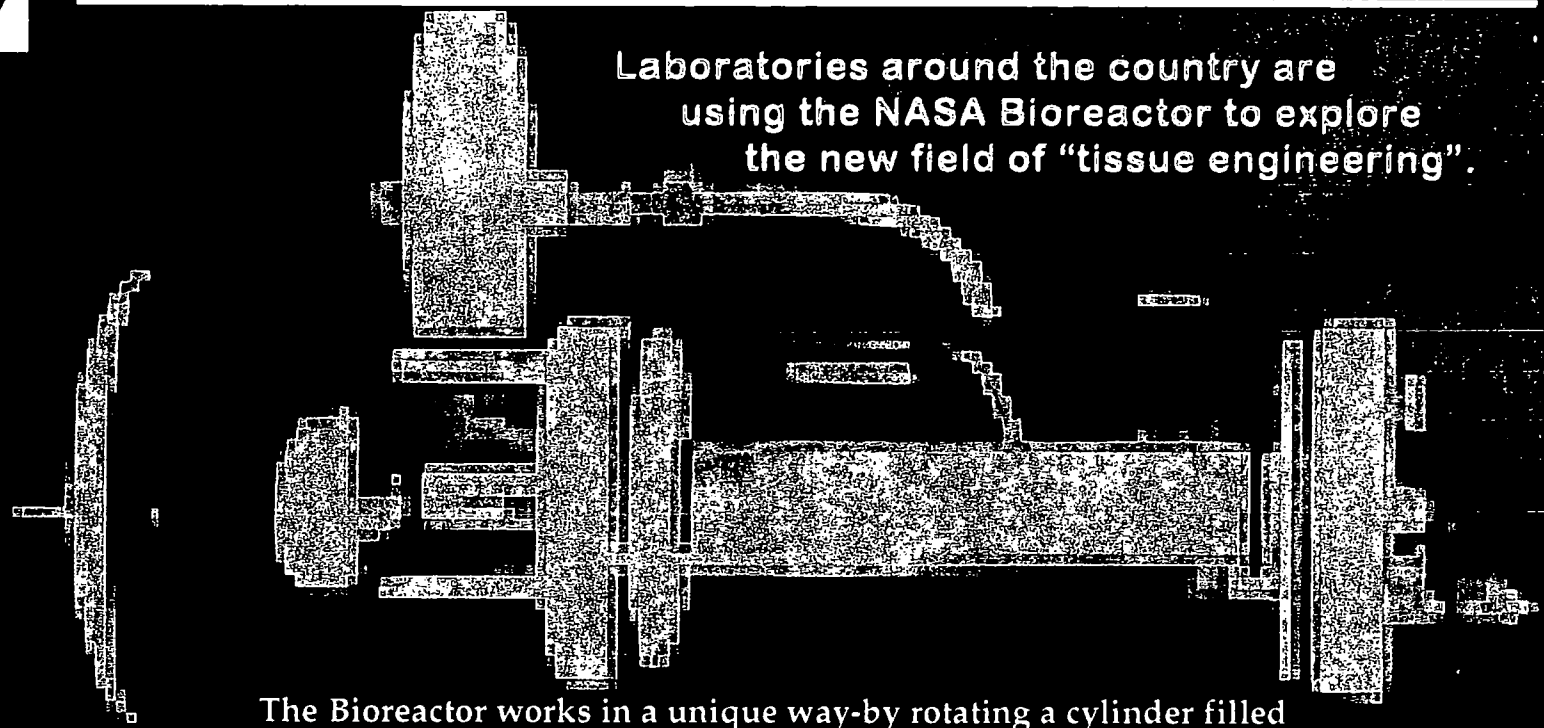




The NASA bioreactor is an incredible device which allows us to grow human tissue outside the body. This may allow us to discover how to grow tissues suitable for transplantation!

The Bioreactor

Laboratories around the country are using the NASA Bioreactor to explore the new field of "tissue engineering".



The Bioreactor works in a unique way-by rotating a cylinder filled with nutrients in order to suspend cells. It's this suspension and the flow of fresh nutrients to the cells that allows the growth of 3-dimensional tissues. However, fast rotation needed on the Earth adds stress to the tissue, and growth size becomes limited. In space, the Bioreactor needs only to rotate slowly in order to refresh nutrients. Tissues can therefore grow larger, more closely resembling those in the human body.

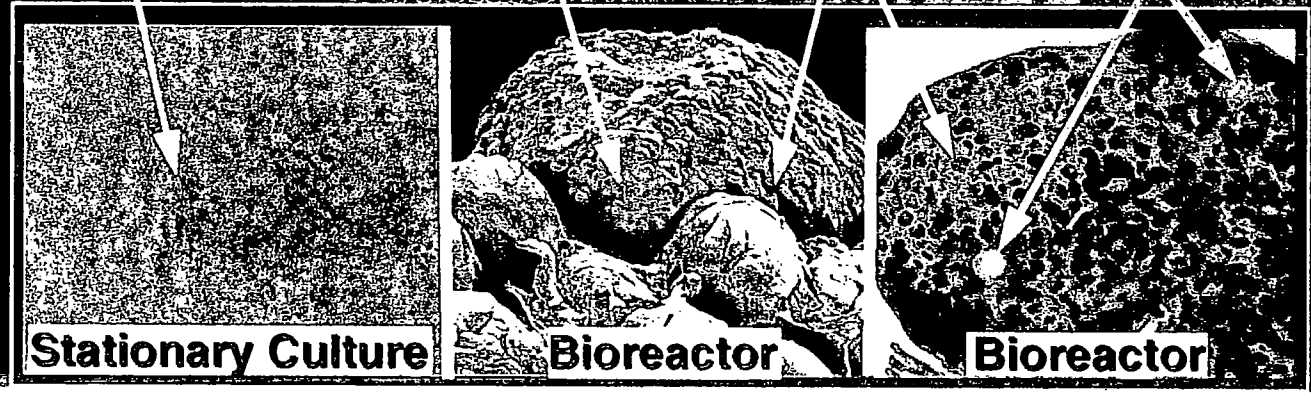
Using the Bioreactor, researchers may discover how to grow tissue suitable for transplantation. It may also provide insight into how cancer cells grow into tumors, how tumors spread to other organs, and possibly how to prevent both of these events.

Modeling Colon Cancer
an experiment in 3-D

With 166,000 new cases diagnosed each year in the US alone, colon cancer is the second most common cause of death.

As opposed to traditional stationary cultures, 3-D colon cancer tumors grown in the Bioreactor closely resemble tumors extracted from humans, including polyps and gland-like parts (see below).

It is the study of the behavior of these tissues outside of the human body which may allow researchers to understand how cancer spreads, as well as identifying new therapies which may prevent it.



THE FORUM

Time for the leap to Mars

We can do it now — no great breakthroughs, science-fiction futurism or gargantuan technologies, just some brass-tacks engineering. And we must do it now — for the knowledge, the challenge and our future.

By Robert Zubrin

The time has come for America to commit itself to a bold new venture in space: the human exploration and settlement of Mars. We're ready.

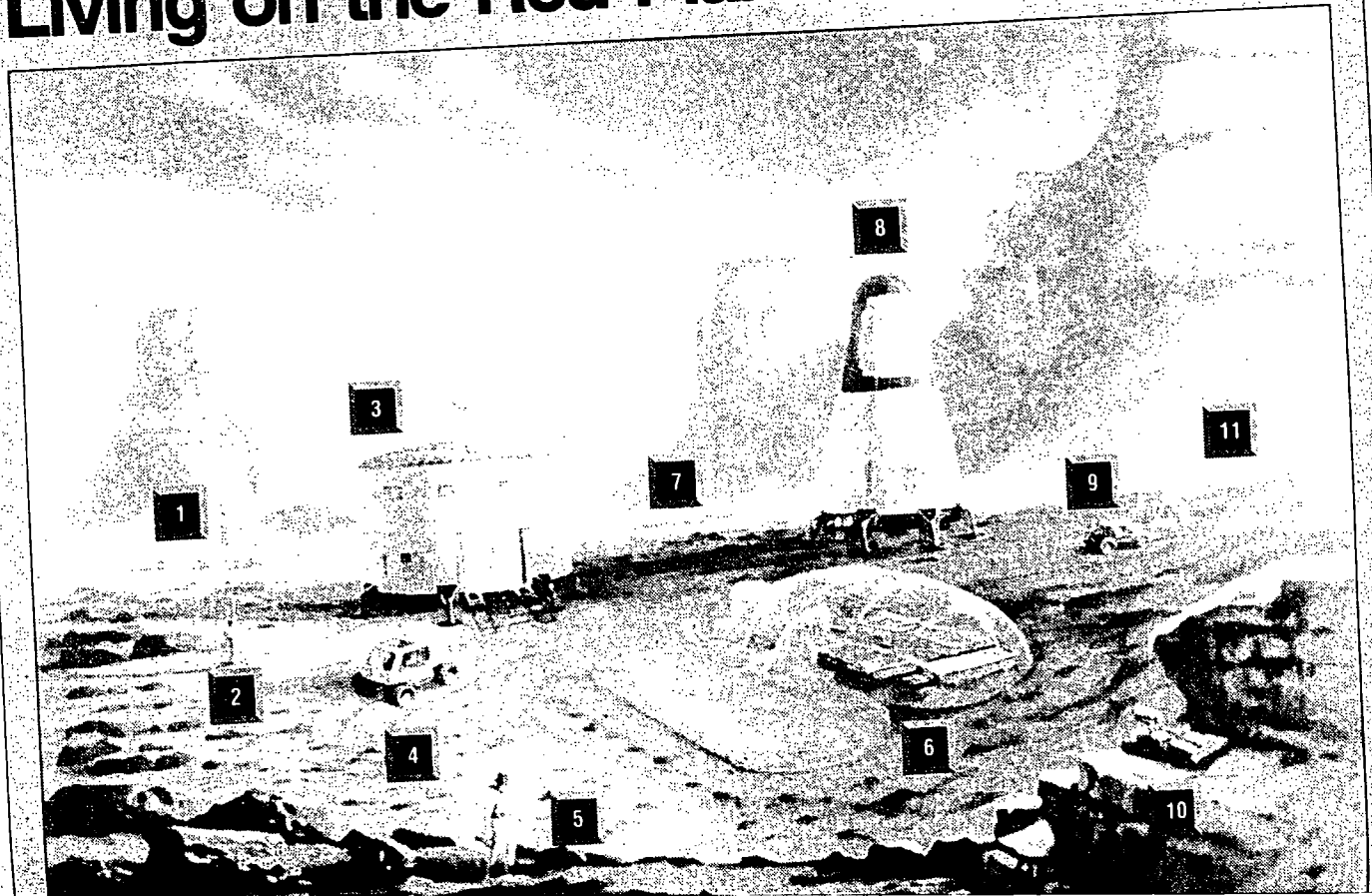
Despite the greater distance to Mars, we are much better prepared today to send humans to Mars than we were to launch humans to the moon in 1961 when John F. Kennedy challenged the nation to achieve that goal. Given the will, we could have our first teams on Mars within 10 years.

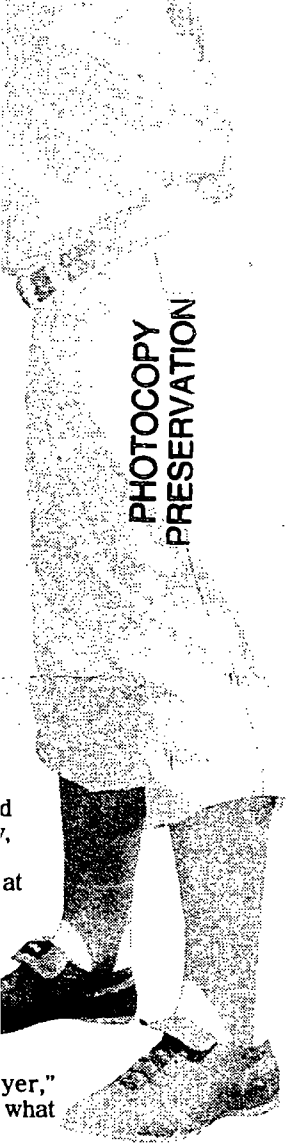
It needn't break the bank, either. Sure, it's possible to design an exploration program that's impossibly costly, and in 1989 NASA did exactly that with its $450 billion response to President Bush's call for a space exploration initiative.

The NASA 1989 plan was so expensive because it involved developing orbiting spaceports to construct giant interplanetary spaceships filled with all the supplies needed for a round trip to Mars.

But there are much smarter and cheaper ways to fly human Mars missions. The key is to adopt the pioneer's philosophy: "Travel light and live off

Living on the Red Planet





By Harry Harris, AP

Jackie Robinson

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Nike ads "Golf's an invitation"
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the land."

Here's how it could be done: In 2005 we launch a single heavy lift booster off the Cape and use it to throw to Mars an unfueled and unmanned Earth Return Vehicle (ERV). After landing on Mars, the ERV runs a pump to suck in the Martian air — mostly carbon dioxide — and mixes it with a small amount of hydrogen brought from Earth to produce a large supply of methane/oxygen rocket propellant.

Then, in 2007, another booster is used to shoot the crew out to Mars. Because their return ride is waiting for them on the planet's surface, the crew does not need to fly to Mars in a giant, futuristic spaceship. Instead, a basic habitation module would do. The crew lands their hab on Mars in the vicinity of the ERV and uses it as their house for a year and a half while they explore the Red Planet. At the end of that time, they get in the ERV and fly home, leaving the hab behind on Mars. Thus, as one mission follows another, more habs are added to the base, building up mankind's first foothold on a new world.

That's it. No great breakthroughs, science-fiction futurism or gargantuan technologies are needed, just some good, brass-tacks engineering, some 19th century industrial chemistry and a little bit of moxie.

The cost: about $20 billion to develop all the hardware needed. After that, each mission would cost between $1 billion and $2 billion. Twenty billion is not a trivial sum, but over 10 years it would represent about 15% of NASA's budget, or less than 1% of the U.S. military budget. It's a sum that this country easily can afford.

But why do it? There are three reasons.

▶ **Reason 1:** For the knowledge. This past summer, NASA scientists revealed a rock ejected from Mars by meteoric impact which showed strong evidence of life on Mars in the distant past. If this discovery

By Robert Murray, Pioneer Astronautics

We're better prepared to pioneer Mars today than we were to explore the moon decades ago. Here's how it might be done:

1. **Solar panels**: For backup power for the base.
2. **Drill rig**: To probe into the Martian subsurface for liquid water. Such water may be the home of Martian life. If hot, it could also be a future source of geothermal power.
3. **Hab module**: The home for four astronauts during their 6-month trip to Mars and their 1.5-year stay on the Martian surface.
4. **Pressurized ground rover**: For use in extended field trips away from the base. The pressurized rover could house two astronauts for a week in a shirt-sleeve environment.
5. **Astronaut**: Equipped with a geological tool kit, chemical analysis gear, and other instruments, human explorers could search for fossils and perform a detailed survey of the Martian surface.
6. **Inflatable greenhouse**: Members of the first mission could test Martian soils for agricultural productivity. Later missions could harvest any crop to augment their food supply.
7. **Nuclear reactor**: Could provide the primary source of base power.
8. **Earth Return Vehicle**: Fueled from the Martian air utilizing old-fashioned chemical engineering processes, the ERV could provide a home for the astronauts during their 6-month voyage from Mars back to Earth.
9. **Unpressurized rover**: This hot rod could provide spacesuited astronauts with mobility for trips as far as 40 miles from the base.
10. **Instrument package**: Used to measure atmospheric and seismic conditions, this instrument package would feature a camera to allow viewers on Earth to monitor the activities of the Martian base.
11. **Balloon**: Astronauts could use balloons to loft instruments long distances from the base. Driven by the fast Martian winds, the balloons would be able to perform aerial photography and land remote-controlled rovers in otherwise inaccessible locations.

By Genevieve Lynn, USA TODAY

quires the human ability to travel long distances through unimproved terrain, to climb steep slopes, to do heavy and delicate work, and to exercise very subtle forms of perception and on-the-spot intuition.

▶ **Reason 2:** For the challenge. Nations, like people, thrive on challenge and decay without it. The space program itself needs challenge. Consider: Between 1961 and 1973, under the impetus of the moon race, NASA produced a hundred times the rate of technological innovation it has shown since, for an average budget in real dollars only about 20% more than today. Why? Because it had a goal that made its reach exceed its grasp. You don't need to develop anything new if you are not doing anything new. Far from being a waste of money, forcing NASA to take on the challenge of Mars is the key to giving the nation a real technological return for its space dollar.

A humans-to-Mars program also would be a challenge to adventure to every kid in the

▶ **Reason 3:** For the future. Mars is not just a scientific curiosity; it is a world with a surface area equal to all the continents of Earth combined, possessing all the elements that are needed to support not only life, but also technological civilization. As hostile as it may seem, the only thing standing between Mars and habitability is the need to develop a certain amount of Red Planet know-how. That will be done by those who go there first.

Mars is the New World. Someday millions of people will live there. What language will they speak? What values and traditions will they cherish, to spread from there as humanity continues to move out into the solar system and beyond? When they look back on our time, will any of our other actions compare in value to what we do today to bring their society into being?

Today we have the opportunity to be the founders and shapers of a new and dynamic branch of the human family. It is a privilege not to be dis-

History of man, Mars

The exploration of Mars has been a goal since the beginning of the U.S. and Soviet space programs. It was the first planet probes were sent to and has been the second most visited after Venus. U.S. and Soviet Mars probes and their results:

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By Harry Harris, AP

Jackie Robinson

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's picture: "He was the
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the Philadelphia Daily
board of contributors.

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But why do it? There are three reasons.

▶ **Reason 1:** For the knowledge. This past summer, NASA scientists revealed a rock ejected from Mars by meteoric impact which showed strong evidence of life on Mars in the distant past. If this discovery could be confirmed by actual finds of fossils on the Martian surface, it would show that the origin of life is not unique to the Earth and, thus, by implication, reveal a universe that is filled with life and probably intelligence as well. From the point of view of humanity learning its true place in the universe, this would be the most important scientific enlightenment since Copernicus.

Now, robotic probes can help out in such a search but by themselves are completely insufficient. Fossil hunting requires the human ability to travel long distances through unimproved terrain, to climb steep slopes, to do heavy and delicate work, and to exercise very subtle forms of perception and on-the-spot intuition.

▶ **Reason 2:** For the challenge. Nations, like people, thrive on challenge and decay without it. The space program itself needs challenge. Consider: Between 1961 and 1973, under the impetus of the moon race, NASA produced a hundred times the rate of technological innovation it has shown since, for an average budget in real dollars only about 20% more than today. Why? Because it had a goal that made its reach exceed its grasp. You don't need to develop anything new if you are not doing anything new. Far from being a waste of money, forcing NASA to take on the challenge of Mars is the key to giving the nation a real technological return for its space dollar.

A humans-to-Mars program also would be a challenge to adventure to every kid in the country: "Learn your science and you can become part of pioneering a new world." There will be more than 100 million kids in our nation's schools over the next 10 years. If a Mars program were to inspire just an extra 1% of them to scientific educations, the net result would be 1 million young, developed minds creating new industries, finding new medical cures, strengthening national defense, and increasing national income to an extent that dwarfs the expenditures of the Mars program.

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Today we have the opportunity to be the founders and shapers of a new and dynamic branch of the human family. It is a privilege not to be disdained lightly.

Last August, in the wake of the announcement of the Mars meteorite discovery, President Clinton had a near encounter with greatness when he issued a call for a "space summit" to plan a possible full-scale assault upon the Red Planet. However, the summit has been continually postponed, and it now appears to have disappeared from the agenda altogether. This is a mistake; a historic opportunity is being missed. We have a space program that needs to be mobilized, a generation that needs to be inspired, and a new frontier that needs to be opened. The bold launching now of a humans-to-Mars program will do all of these things.

Mr. Clinton: Seize the time.

Robert Zubrin, an astronautical engineer, is executive chairman of the National Space Society and author of The Case for Mars: The Plan to Settle the Red Planet and Why We Must.

By Genevieve Lynn, USA TODAY

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- ▶ **July 1988** Soviet Phobos 1, contact lost
- ▶ **July 1988** Soviet Phobos 2, seventh Mars orbiter, contact lost
- ▶ **Sept. 1992** U.S. Mars Observer, contact lost
- ▶ **Nov. 1996** U.S. Mars Global Surveyor, arrives Oct. 1997
- ▶ **Nov. 1996** Russian Mars-96, crashed into South America
- ▶ **Dec. 1996** U.S Mars Pathfinder, arrives July 1997, will be first land rover to land on Mars

Source: Jane's Space Directory