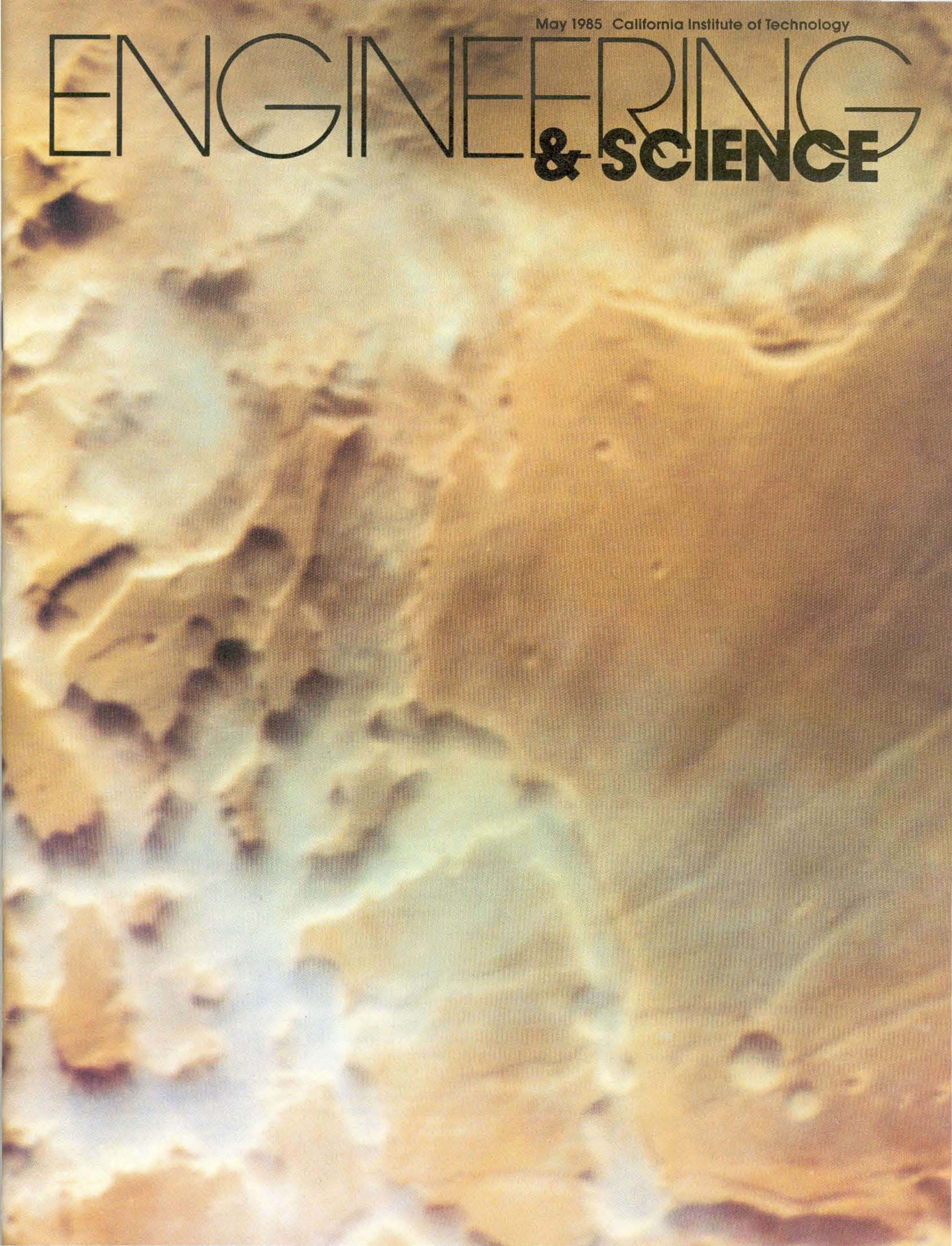
May 1985 California Institute of Technology

ENGINEERING & SCIENCE



In This Issue

Mars-scape

On the cover — in the early morning on Mars, water-ice clouds form in the small canyons of Noctis Labyrinthus, a high plateau. Viking Orbiter 1 captured this idyllic Martian landscape in July 1976; the scientists at JPL processed the image and enhanced the color. It's one of 140 images in Baxter Art Gallery's current (and final) exhibition "25 Years of Space Photography: Jet Propulsion Laboratory, California Institute of Technology."

All of the images were transmitted from NASA's unmanned space exploration missions and processed for NASA by JPL, creating pictures of "extraordinary scientific value," according to JPL director Lew Allen. They are also images of extraordinary beauty and seem entirely appropriate on the walls of an art gallery.

The quarter-century JPL retrospective will run at Baxter through July 31. Several selections from the show appear on pages 15-19.

Counting Chromosomes

"Human Chromosomes — Down's Disorder and the Binder's Mistakes," which begins on page 8, was drawn from Dan Kevles's new book, *In the Name of Eugenics: Genetics and the Uses of Human Heredity.* Much of the book appeared in three installments in *The New Yorker* last fall as "Annals of Eugenics: A Secular Faith." Most of the article printed here, however, did not; *E&S* is pleased to be able to offer what *The New Yorker* chose to leave out.

Kevles has published numerous articles on the history of science, and his previous book, *The Physicists: The History of a Scientific Community in Modern America*, won the National Historical Society Prize in 1979 and was nominated for an American Book Award. Professor of history since 1978, Kevles joined the Caltech faculty in 1964, the same year he received his PhD in history from Princeton. His BA is also from Princeton (1960) — in physics.

Spurning Embers

The football field's bleachers were filled one sweltering Sunday in April with people watching a demonstration of firewalking. Sponsored by the Southern California Skeptics, a group that draws many of its members from the Caltech community, the demonstration debunked the claim that special mental or mystical preparation is required for this feat. The Skeptics society is profiled in "Ghostbusters!" beginning on page 2, written by an *E&S* staffer. The writer himself did not walk on the coals. When asked why, he replies, "What — and compromise my journalistic objectivity?"

Simon Says

Barry Simon came to Caltech from the Princeton faculty in 1980, first as a Sherman Fairchild Distinguished Visiting Scholar and the following year as professor. Last fall he was named the IBM Professor of Mathematics and Theoretical Physics. His PhD is also from Princeton (1970) and he received his BA from Harvard in 1966.

Simon has published nearly 200 papers and 9 books in areas ranging from pure mathematics to theoretical physics to physical concepts. His theorems have contributed significantly to the recent revolution in theoretical chemistry and theoretical atomic and molecular physics. In 1981 he received the medal of the International Academy of Atomic and Molecular Science.

He's regarded as an expert on Schrödinger operators, which have relevance to both mathematics and physics, and which he heroically offered to attempt to explain to *E&S* readers. His article, "The Theory of Schrödinger Operators: What's It All About?" begins on page 20.

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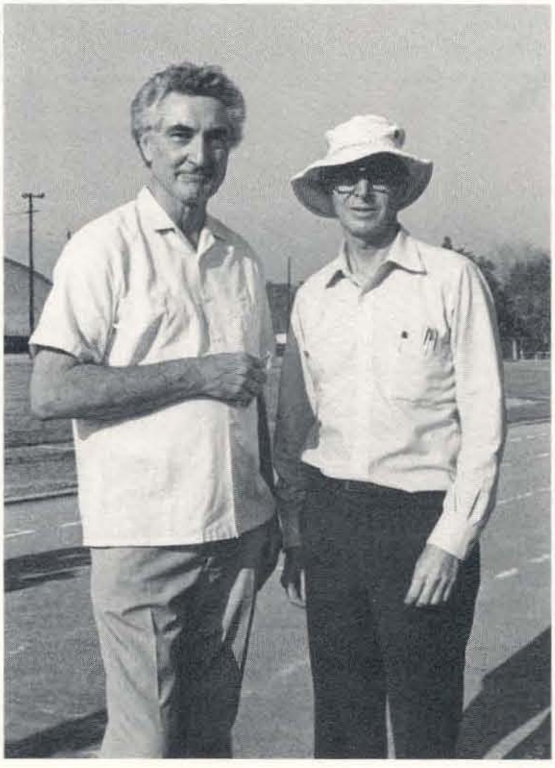
Ghostbusters!

THEY DON'T WEAR FUNNY UNIFORMS, they don't store ectoplasm in the basement, and not one of them has ever been "slimed." They don't even have a video on MTV. Yet a recently formed group called the Southern California Skeptics (SCS), with a strong base of support among the Caltech community, has been remarkably successful in causing ghosts of one sort or another to evaporate. In so doing, they have literally walked through fire, and they have repeatedly exposed themselves to that most terrifying and voracious of modern apparitions — the American news media.



The Skeptics society has several Caltech stalwarts on its board, among them Al Hibbs (BS '45, PhD '55) and Paul MacCready (MS '48, PhD '52).

Affiliated with a national organization called the Committee for the Scientific Investigation of Claims of the Paranormal (aptly acronymed CSICOP), SCS has grown quickly in the few months of its existence. Its board of directors includes Caltech faculty members Murray Gell-Mann and Joseph Kirschvink, JPL's Albert R. Hibbs, professors from USC and UCLA, and professional magicians. The group's stated aim is to promote the fair and accurate investigation of claims of alleged paranormal occurrences and to disseminate the results of these investigations. SCS has staged a number of well-attended lectures and demonstrations on the Caltech campus on such subjects as psychic surgery, the Bermuda triangle, and Kirlian photography, and has received quite a bit of (mostly) favorable media attention.

Glendower: I can call spirits from the vasty deep.
Hotspur: Why, so can I, or so can any man;
But will they come when you do call for them?
—Shakespeare, *Henry IV, Part I*

But there have been some growing pains. The Skeptics' first foray onto local television was not a notable success. KABC's *Eye on L. A.* program invited SCS chairperson Al Seckel and several members of the board — Dennis Marks and Sandy Spillman (both

magicians) and Ronald Crowley (formerly a Caltech visiting associate in physics and now a Cal State Fullerton professor) — to investigate videotapes and still photographs, taken at a Westwood cemetery, that contained mysterious images of ghostly ectoplasm.

The videotape, made in dim light near a grave at the foot of a tree, showed odd fluctuations of light at the same time that a psychic who was present claimed to be sensing a lady ghost, dressed 1920s-style in a red hobble skirt. The still photograph, made near the same tree, contains several streamers of ectoplasmic light, apparently emanating from the grave itself. Given just 30 minutes to examine the evidence and interview the film crew before commenting, on camera, about their findings, the Skeptics were unable to find a simple explanation for the images. When the show was aired, the producers felt justified in calling the images not just "unexplained," but "unexplainable."

With just a little further investigation, however, the Skeptics were able to explain the unexplainable. The fluctuations in light in the videotape were caused by a camera operating below its threshold of sensitivity in the dim light. At an amplification factor of 64, tiny fluctuations in available light caused large fluctuations in the image. And the streamers of light in the still photo were the result of this camera being jerked while its shutter stuck open. Despite repeated requests, however, the show's producers refused to allow the Skeptics to present these findings.

> Can one go upon hot coals, and his feet not be burned?
>
> —Proverbs 6:28

The Southern California Skeptics received more favorable media coverage one recent spring Sunday when they staged a demonstration of firewalking at Caltech's football field. The bleachers were filled with spectators as over a hundred people walked on an eight-foot bed of 1000° F coals, most emerging unscathed.

In recent months the airwaves have been filled with reports of firewalking exhibitions, staged by groups who, for fees ranging from a hundred to several thousand dollars, purport to teach participants the mind-over-body techniques that they claim are necessary for

UCLA professors Bernard Leikind and William McCarthy decide who will walk first on the 1000° F coals. In the end, over 100 people performed this seemingly miraculous stunt, including (from left) Caltech students and former students Dan Harrison, Jeff Matus, Rod Schmidt, Brad Solberg, and Rajeev Krishnamoorthy.

performing this apparently perilous stunt.

These firewalking seminars intrigued two UCLA professors — physicist Bernard J. Leikind and psychologist William J. McCarthy. Both members of the Southern California Skeptics, they were, well, skeptical to say the least and decided to put the seminar to the test. One evening last November McCarthy attended one of these seminars in Burbank while Leikind waited outside. And then *both* walked safely on the coals, proving that the intensive, six-hour motivational seminar was unnecessary.

It turns out that the ability to walk on hot coals can be explained by physical law; it isn't necessary to resort to mysticism or any mysterious psychological process. The explanation depends on the difference between *temperature* and *heat*. Imagine a cake baking in an oven at 450°. You can reach your hand into the oven and touch the cake without being burned, but you'll be burned instantly if you touch the aluminum pan it's baking in. The pan and the cake are at exactly the same temperature, but the cake has a low heat capacity and poor thermal conductivity, while the pan has a high heat capacity and good thermal conductivity. The wood coals used in firewalking demonstrations conduct heat poorly and, as long as a walker moves over them reasonably quickly, the feet will cool the coals more than the coals will heat the feet.

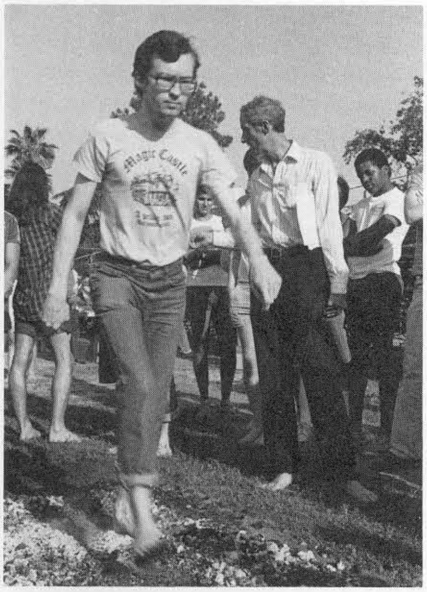
> Skeptics laugh in order not to weep.
> —Anatole France

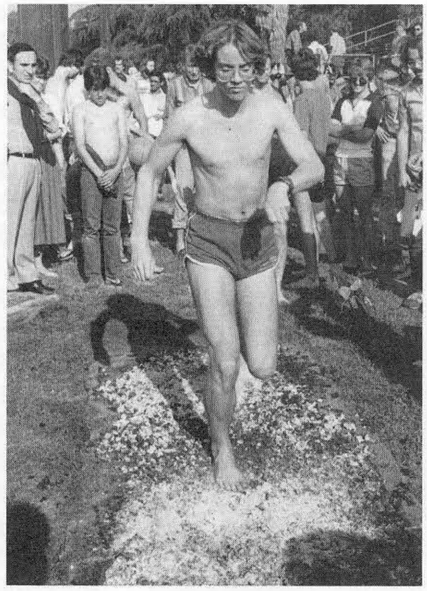
Media attention has led to a rapid expansion in Skeptics society membership, but it has also led to more than a few crank calls. CSICOP founding member James Randi, the well-known magician who's also an SCS board member, has a standing offer of $10,000 for proof of any paranormal, supernatural, or occult power demonstration under properly controlled conditions, and this too prompts some rather interesting conversations. One woman phoned SCS, for example, claiming to have the power to make it rain in her Seal Beach neighborhood within any 24-hour period without fail. She was challenged to make it rain the very next day, but the next day was dry. She called back to say that it hadn't rained in Seal Beach because she had mistakenly caused it to rain in Louisiana, and she asked for SCS's "certificate of approval" so that she could be sent to Africa to help relieve the drought.

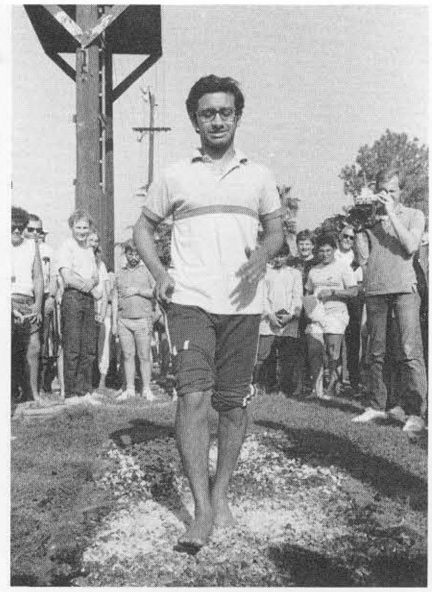
Another caller claimed that his pencil was omniscient and directed his hand, writing what it wished. Al Seckel thereupon asked the pencil to solve a simple math problem: the derivative of x^2. The all-knowing pencil apparently never took calculus, since it couldn't come up with the answer.

And another caller claimed to know for a fact that Bigfoot was real. When Seckel asked why Bigfoot had never been shot, given the large number of hunters who have searched for him over the years, the caller replied that Bigfoot *had* been shot, and more than 500 times too. In that case, Seckel queried, why has a carcass never been found. "That's how we know he's paranormal," replied the caller.

> The ultimate result of shielding men from the effects of folly is to fill the world with fools.
> —Herbert Spencer





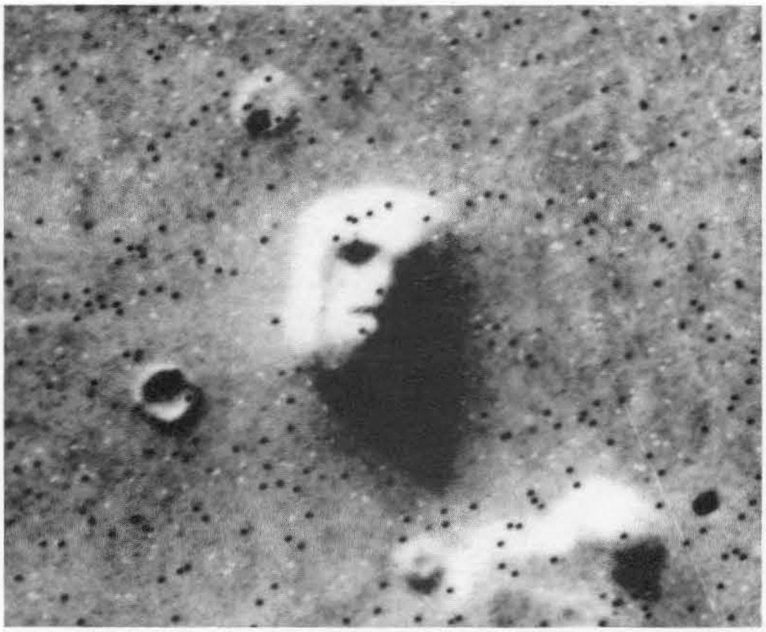


While debunking fraudulent or misguided claims is fun and receives the greatest amount of media attention, most of the Skeptics would agree that debunking is not the main goal of the society. Al Hibbs, a senior staff scientist at JPL and a member of the board of the Southern California Skeptics, says, "the major goal is to encourage people to think about seemingly marvelous, mystical, and miraculous phenomena rather than just accepting the notion that they're supernatural. We're trying to encourage people to adopt a scientific attitude, to investigate a little bit. We're not particularly interested in debunking things, although if it comes to that, fine. The primary thing we want to do is encourage people to adopt a way of thinking, a scientific attitude to what happens in daily life, to doubt whether the answer first presented is the right one, to examine alternative explanations." In his position at JPL, Hibbs manages a group engaged in research and instrument development for future unmanned space missions. Given his involvement in astronomy, it's understandable that he has a particular interest in investigating the subject of astrology. "I'm a Libra," he says. "Libras don't believe in astrology."

An interesting perspective on the proper goals of the skeptic is provided by Murray Gell-Mann, the Robert Andrews Millikan Professor of Theoretical Physics and a member of the boards of both SCS and CSICOP. He says, "My friends and acquaintances in this movement choose to designate their particular targets as 'claims of the paranormal.' Most of these people share with me the belief that there is no such thing as the paranormal. That is to say, whatever actually happens in fact can be described within the framework of science. If something new is found that doesn't fit with our present laws of science, we wouldn't throw up our hands. What we would do is to enlarge or otherwise modify the laws of science to incorporate the new phenomenon.

"That puts us in a strange logical position if what we are doing is investigating claims of the paranormal, because in the end nothing is paranormal. It means, basically, that what we are doing is encouraging the skeptical examination of screwy phenomena in general, and some of them are bound to turn out to be basically genuine. So the debunking spirit, while it's entirely appropriate for most of these things, is not a perfectly satisfactory general approach.

Some of the firewalkers did end up with hot feet. Here, Caltech senior Jeannine St. Jacques cools her tootsies after her attempt.



The unskeptical have made much of this top photo, taken by the Viking 1 Mars Orbiter. Intelligent Martians, they say, must have carved the humanoid features into this huge rock formation. Appearances can be deceiving, though. The face's right nostril, its chin dimple, and much of its right eye are dropped data bits, not actual surface features. The human brain has a propensity for perceiving faces, even in random patterns. Another example is a Martian lava flow (bottom) that looks like Kermit the Frog. If the Martians sculpted Kermit, why'd they leave out Miss Piggy?

"There's a classification of genuineness that's useful here. First of all there are things that turn out to be caused by conscious fraud — psychic surgery, things of that kind. Next, we have results of error but not demonstrably conscious fraud." According to Gell-Mann, many superstitous beliefs fall into this category and have as their basis, "poor or mistaken observations, a tendency to remember evidence in favor of a hypothesis, bad statistics, and lack of care in searching for natural explanations.

"Then we can go on from these classes of claims that are basically false to claims that turn out to be true. Some of them have simple explanations from physical science, as turned out to be the case for firewalking. There, the most important result is that firewalking is perfectly possible. It's not a false claim; it's not a psychosomatic effect; it's simply a physical one.

"But there are some phenomena that apparently *are* of the psychosomatic category. The placebo effect (in which objectively worthless treatments help in fighting serious disease) is the most famous. To reduce something to the placebo effect is not to show that it's unimportant or not there. The placebo effect is one of the most important in medicine and needs to be better understood. There are, of course, also some remarkable genuine effects that are biological or psychological in character but not psychosomatic.

"To go further, what about claims that would require, if they were substantiated, some quite novel ideas that are unfamiliar to science? And those claims I would attempt to classify into two kinds: those that involve very complicated environmental situations where we don't know for sure what the results of the fundamental underlying laws of science would be, and those that seem to require the revision of the most fundamental laws."

In the first of these categories, Gell-Mann puts the famous historical case of the meteorites. For hundreds of years scientists scoffed at the seemingly ridiculous idea that rocks could fall from the sky. This disbelief persisted until 1803, when an undeniable shower of stones fell on L'Aigle, a town close to Paris and close, therefore, to the leading scientists of the day. According to Gell-Mann, a modern example of this may be, "the persistent, although rare, reports of falls of fish and other relatively large creatures from the sky. The anecdotal reports are relatively consistent, come from reliable observers, and may well be true. And meteorology contains enough richness that they can probably be explained. We should not, in such a complicated situation, reject the possibility of something being true because we can't think of a mechanism based on the fundamental laws we know. We shouldn't try to debunk it. We should go out and study the evidence and see if there is such a thing. We should be skeptical, of course, but there's no reason to adopt what I call the 'debunking mode.'

"Finally we get to the last category — those phenomena that seem, as far as we can tell, to contradict the most fundamental principles and would require, if genuine, really major revisions of scientific law. For these, of course, we must have a very healthy dose of skepticism. Probably most phenomena that would be described by the name extrasensory perception would be in this category if they turned out to be true, which I think is extremely unlikely. But these reports, persistent as they are, should be examined, to see what comes out of them. And, of course, the usual methods of the skeptic have to be applied. Although it's likely that phenomena of that sort will dissolve under skeptical examination, we should bear in mind the possibility that some might survive and find explanation in new scientific laws.

"Suppose, for example, it turned out to be true, as is often claimed, that pairs of people linked by special bonds, such as identical twins or mother and daughter, can communicate with each other telepathically, almost independently of distance, in moments of stress. We would have to start formulating and testing scientific hypotheses about how that could occur. Is there, for example, some new kind of material cord connecting such people, which gets 'twitched' at times of great anguish? Of course, it is most likely that nothing is there except chance and selective recollection.

"The whole notion of dealing with the paranormal dissolves a little bit under this analysis. We should encourage the study of all kinds of claims, with different doses of skepticism in different cases, and try to see what comes out of careful observation. When it looks as if conscious fraud is involved, with people being exploited to their harm, as in the case of psychic surgery, debunking is the right mind set, the right tone of voice. In other cases, it's a question of showing how thin the evidence is. In still others, we may want to pursue the matter vigorously to see if there is not really something in it, whether simple natural science, sophisticated natural science, complex environmental science, or (what is very improbable) a major revision of fundamental scientific laws. In certain cases, it is the gullibility or trickiness of people involved that turns out to be interesting, or the preference for supernatural over scientific explanations, or the deliberate sensationalism of the news media.

"In all cases, though, I believe our emphasis should be on trying to understand what is going on."

> The fact that a believer is happier than a sceptic is no more to the point than the fact that a drunken man is happier than a sober one. The happiness of credulity is a cheap and dangerous quality.
>
> —George Bernard Shaw

> The most costly of all follies is to believe passionately in the palpably not true. It is the chief occupation of mankind.
>
> —H. L. Mencken

Why *do* people seem to prefer supernatural explanations? This is a question that interests many of the Skeptics. Gell-Mann says, "Great numbers of people believe in all these things with insufficient evidence either because they falsely believe there is sufficient evidence or, in more cases, because evidence is not an important criterion to their belief. In fact, many people state the matter in the following way: that one should believe what it makes one feel good to believe. This is not to say that such belief is worthless. Faith in things that are probably not true can be very powerful; it can, in some cases, give people strength or courage or a relaxed and confident attitude that permits them to accomplish tasks that would otherwise be too difficult. I would like to think that the same kinds of results can be achieved without belief in the supernatural." Hibbs advances the answer that magical thinking is a shortcut way of dealing with the world. "If you can make something happen just by thinking about it, that's much easier than having to go to work." And he also says, "Psychic phenomena have, always off there in the background, immortality, life after death, that magic thinking."

But those who have studied science realize that scientific explanations of natural phenomena are often far more elegant and far more beautiful than the most fanciful, magical, or supernatural interpretations that people have concocted over the centuries. Perhaps the best thing to do is to recite, each night before going to bed, the ancient Scottish supplication that might be called the Skeptic's Prayer:

> From ghoulies and ghosties and long-
> leggety beasties,
> And things that go bump in the night,
> Good Lord deliver us! □

— *RF*

For more information on the Southern California Skeptics or CSICOP, contact SCS at P.O. Box 7000-39, Redondo Beach, CA 90277, 213-540-0915.

Human Chromosomes — Down's Disorder and the Binder's

by Daniel J. Kevles

This article, part of which appeared originally in The New Yorker, *is drawn from Kevles's new book,* In the Name of Eugenics: Genetics and the Uses of Human Heredity, *which was published this month by Alfred A. Knopf, Inc. As the "first book to deal seriously and objectively with the development of human genetics as a scientific and medical discipline," Kevles's account of the application of heredity theories to "improving" the human race also examines the controversial social, moral, and political issues that descended from it — from the origins of eugenics in the late 19th century up to the present.*

IN AUGUST 1955, Joe-Hin Tjio, a young Indonesian who was then working in Zaragoza, Spain, came to Lund, Sweden, for one of his periodic collaborations with Albert Levan. Both were primarily plant cytologists, but now their attention was turned to the chromosomes in the human cell. The nucleus of the normal human cell contains two sex-determining chromosomes — *XX* for females and *XY* for males — plus 22 pairs of autosomes — that is, chromosomes unrelated to sex. The total comes to 46. That fundamental number of human cytogenetics was established by Tjio and Levan during Tjio's visit in 1955 — long after cytologists had started counting the chromosomes of man in the 1890s.

The very early counts had yielded numbers that varied around 24, which was consistent with those obtained for other mammals. The trouble then was that cytologists made their counts with tissue taken from corpses, often those of executed criminals; upon the death of mammalian cells, the chromosomes tend to clump together rapidly, thus deceiving even the microscope-aided eye into falsely low counts. Recognizing the problem, the Belgian cytologist Hans von Winiwarter used fresh tissue obtained during surgery and immediately fixed with a chemical preparation. In 1912, he reported the human chromosome number to be 47 for males and 48 for females. Von Winiwarter explained the sexual difference by arguing that while the human female had two sex chromosomes — a double *X* — the human male must have only one, a single *X*.

Von Winiwarter's result, neither confirmed nor rejected, was evidently regarded as an anomaly by most cytologists, but at the beginning of the 1920s his use of fresh tissue caught the attention of Theophilus S. Painter, a cytogeneticist at the University of Texas.

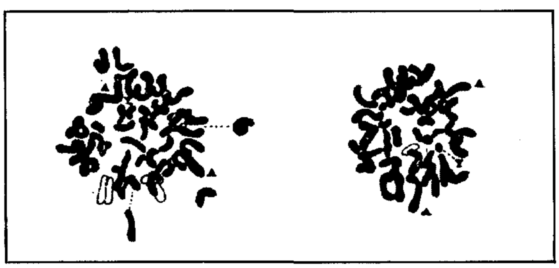
Mistakes

One of Painter's former students happened to be practicing medicine at the state mental institution in Austin. Painter obtained the testes from three patients — one white, two black — all of them castrated, Painter reported, because of "excessive self-abuse coupled with certain phases of insanity." Within a few minutes of their removal from the blood supply, the specimens were slit into multiple sections and dropped into a fixing solution. In mid-1921, Painter reported to a colleague that "my best counts now give me 48 chromosomes for both the Negro and white man. . .and [I] feel confident that this is correct." Perhaps his confidence derived from the fact that the figure squared with von Winiwarter's for females. More important, as in other mammals, the total included the male sex-chromosome combination, *X* and *Y*. It was also consistent with his counts in spermatocytes, which, as the products of sexual division, should have contained half the number in non-sex cells, and, so far as Painter saw, did have 24. After Painter published a full report of his work in 1923, other cytogeneticists confirmed his count. For the next 30 years, just about everyone believed the human chromosome number to be 48, for both sexes.

In retrospect, the reasons for the persistent miscounting are clear enough. Normally, the chromosomes lie in a region of the cell nucleus that takes on a deep color upon staining. In the quiescent cell, the individual chromosomes cannot be visually differentiated from the region. They can only be seen — and counted — in the process of cell division, when they emerge as separate, colored — hence the name — rodlike entities. To obtain a chromosome count, human cells had to be captured and fixed at the moment of division. The more cells in a state of division, the better the prospect for chromosomal observations. Particularly suitable were tissues with rapidly proliferating cells, notably embryos or testes, which are sites of constant cellular division.

Such material, obtained fresh from living bodies, was, to say the least, difficult to come by. Many more human chromosome counts seem to have been done with testes than with ovaries for the simple reason that the taking of ovarian tissue required a major surgical procedure. The human cytogeneticist often had to wait, ready to fix his specimens, outside operating rooms or, in the case of a team that confirmed Painter's count, literally at the foot of the gallows. Once obtained and fixed, the specimens were sliced into thin sections with a fine blade — the blade cutting through the nucleus of a given cell as a knife might cut through an egg in the middle of a meat loaf. Just as successive sections of meat loaf would contain successive slices of egg, successive slices of cell — perhaps two or three — would include serial slices of the complete nucleus. Since the chromosomes were spread through the nucleus, some would wind up in one section, some in the next. The cytologist added the number found in each section to reach the total in the cell. But because of imprecision in where the blade happened to cut, fragments of a chromosome located — and already counted — in one section might turn up as candidates for counting in the next. Then, too, compared to fruit flies, which have four pairs of chromosomes, the human cell nucleus is small and the number of chromosomes large. Even when separated and fixed during cell division, human chromosomes are crowded together. They appeared to cytologists of Painter's era as something like the noodles suspended in a soup — some lying beneath others and difficult to count accurately. It was not easy to decide whether the noodle that resembled an "L" under the microscope was a single bent chromosome or two straight ones.

The cytologist Tao-Chiuh Hsu, who once saw a slide of one of the human testicular sections that Painter had prepared, later wrote:



In the early 1920s Painter found 48 chromosomes in each of these cells — a number that remained unchallenged for 30 years.

"I failed to make any sense of the twisted, crowded, stacked chromosomes. It's amazing that [Painter] even came close!" Every enumeration of human chromosomes required judgment, and judgment left room for conformation to orthodoxy. Human chromosomal counts sometimes suggested a figure different from 48, but most cytologists, expecting to detect Painter's number, virtually always did so. Indeed, the preconception in favor of 48 was so powerful that it operated on Hsu himself when, in 1952, he set off the train of experimental work that led to the revision down to 46.

Hsu had come from Chekiang University, in China, in 1948 to take a PhD at the University of Texas; now a postdoctoral fellow in human cytology at the medical branch of the university in Galveston, he was looking at cell nuclei in preparations of fetal spleen tissue. It was with distinct incredulity, Hsu recalled, that he saw in one of the preparations "some beautifully scattered chromosomes." Similar pretty pictures appeared in other slides, but when he examined additional preparations, the chromosomes "resumed their normal miserable appearance." Hsu guessed that something about the original preparations must have been special. For some months, he sought assiduously to find out what. There was no need for him to hover outside some operating-room door to obtain fresh spleen cells. Plenty were available because the original sample had been subjected to tissue culture — the technique by which cells are kept alive and multiplying in vitro with suitable nutrients. Tissue culture had come into use in cytology laboratories after the Second World War, and it provided a continuous supply of dividing cells. Hsu systematically altered the preparation procedure of one sample after another of the abundant embryonic spleen cells. Nothing worked until April 1952, when he added distilled water to the balanced salt solution commonly used to rinse the tissue specimens before fixation.

This so-called hypotonic solution liberated the chromosomes from the cell spindle — a warp of fibers that form during cell division to guide them on their journey — and it also swelled the cell volume, which allowed the chromosomes more room to separate. Hsu guessed that the preparations in which he had seen the chromosomes so clearly must have been accidentally washed in hypotonic solution before being fixed. Turning accident to advantage, he proceeded to look closely at the human chromosomes — not to check the number but to examine their structure. In many cells, he recalled with some irony, "I had difficulty in getting the count to equal 48." Nevertheless, his vision filtered through the prevailing preconception, Hsu managed to count to Painter's figure. He later confessed to feeling like a football player who returns an interception 40 yards only to find himself "fumbling the ball at the three-yard line."

Hsu's metaphor did him a disservice; at the time, he did not know that he was in a contest with nature for the correct human chromosomal count. Neither, three years later, did Tjio and Levan when they found the right number: Their aim had been to explore in detail the morphology of human chromosomes in lung tissue taken from legally aborted embryos. The difference between their work and that of all previous analysts of human chromosomes was its reliance not only on tissue culture and hypotonic treatment but on two other techniques newly deployed in human cytology. One was the pre-treatment of the cells with colchicine, an alkaloid extracted from the seeds of a crocus-like herb. Colchicine arrests cell division midway through its course, thus providing many more cells to be observed in the process of splitting. It does so in a way that further frees the chromosomes to disperse throughout the cellular volume. And it tends to contract chromosomal size, thus diminishing the likelihood of confusing overlaps. The other was the "squash technique," so named because, instead of being sectioned, the cells to be examined were literally squashed with the thumb under a thin glass plate. With the cell thus flattened into something resembling a pancake, the chromosomes are spread onto a single plane of optical focus. Once Tjio and Levan applied all four techniques in combination to their embryonic lung cells, they immediately saw an unambiguous 46 human chromosomes. Further experiments in the fall and winter of 1955 yielded the same count with high consistency, and in 1956 they published their results, though not without residual anxiety about challenging Painter's much-confirmed number.

Within days of its publication, Tjio and Levan's article was read in England by Charles E. Ford, a cytogeneticist in a radiobiological research unit of the Medical

Research Council located at the British Atomic Energy Research Establishment at Harwell, near Oxford. In connection with studies in leukemia, Ford had worked with mouse and, recently, human cytogenetics. Already adept at the essential techniques of the field, he had in fact helped alert Tjio and Levan to the value of treating specimens with colchicine and hypotonic solution. An Oxford University surgeon, impressed with the clarity of Ford's cytological preparations, had offered to send human testicular material for chromosomal analysis. Ford had passed up the opportunity and, as he read Tjio and Levan, wished he had not. Now Ford and John Hamerton, a colleague at Harwell, swiftly confirmed the count of 46, using fresh human tissue supplied by the Oxford surgeon. The work brought Ford to the attention of the human geneticists in London, where interest in human cytogenetics was rising rapidly.

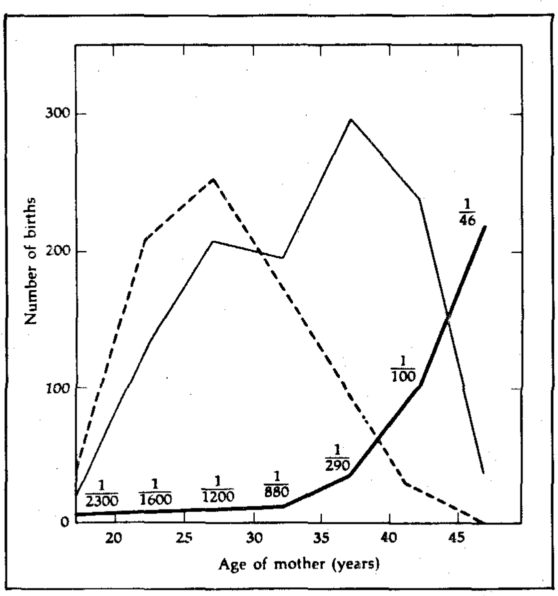
Among those concerned with the subject was Paul E. Polani, a physician at Guy's Hospital on the south side of the Thames, on a sight line from St. Paul's Cathedral. Polani had started in genetics during his undergraduate days in Italy just before the Second World War, and from 1948 to 1950, while on a fellowship, he had spent part of his time at the Galton Laboratory, which was part of University College London and was one of the leading centers in the world of work in human genetics. In 1954, in the course of his research on the causes of congenital heart disease, Polani came across three women who suffered from an aortal defect usually found among males but who also had Turner's syndrome, a condition found almost exclusively among females. Given the characteristics of Turner's syndrome — a thick, webbed neck, shortness of stature, and, especially, rudimentary ovarian and mammary development — Polani wondered whether the Turner's patients might genetically resemble males. At this time, indications of human genetic sex were beginning to be obtained by using the 1949 discovery of Murray L. Barr, a cytologist at the University of Western Ontario: routine staining revealed a small satellite (eventually called a "Barr body") near the nucleolus in the cells of females but not usually of males. Females were thus classified as "chromatin positive," males as "chromatin negative." Polani tested his Turner's females and found that all three were chromatin negative.

This outcome stimulated Polani to further research into human "intersexes" — people of one sex who displayed some characteristics of the other — and he gathered information on 25 more women, about half with Turner's syndrome and the rest with simply no ovarian development. He found 20 of the 25 to be chromatin negative. There was, however, scientific doubt that chromatin negativity could be taken as a definite sign of genetic maleness, particularly among abnormal human beings. Pondering how alternatively to determine the genetic sex of the women, Polani hit upon the ingenious idea of surveying them for a sex-linked trait. Following a discussion of the matter with Lionel S. Penrose, the head of the Galton Laboratory, he resolved to test them for the predominantly male trait of red-green color blindness. He observed this trait in 4 out of the 25 women — a frequency significantly higher than expectation in such a group of genetic females, but one consistent with expectation in a comparably sized sample of genetic males. In his report of these results in *The Lancet*, in July 1956, Polani suggested that the Turner's women might be chromosomally *XO* — that is, might have only one *X* chromosome, instead of the normal female's two.

Polani enlarged his work on color blindness in the human intersexes to include males with Klinefelter's syndrome — a condition with the symptoms of tallness, minor mammary development, and, often, testicular atrophy and mild mental deficiency. Barr and a colleague had just found that Klinefelter's males were chromatin positive — that is, they displayed the nuclear staining feature characteristic of normal females. In October 1958, Polani reported that color blindness occurred among such Klinefelter's with a frequency characteristically observed among females, and he suggested that, like females, Klinefelter's males must have two *X* chromosomes. The question was whether they had a *Y* chromosome, too. There was no way to determine the answer without looking directly at the karyotypes — the word comes from *karyon*, the Greek for "kernel," and signifies the display of chromosomes in the cell nucleus.

In 1955, Polani had tried to determine the genetic sex of a few of his Turner's patients by looking at their karyotypes with the aid of Gordon Thomas, an anatomist at Guy's Hospital who knew how to do tissue cultures. Inexperienced at working with human chromosomes, they obtained — from three Turner's women and seven normal people used as controls — only a handful of complete cell samples, and none of sufficient quality to assess what sex chromosomes the cells contained. (They did manage to count 45 chromosomes in one of the karyotypes but mistrusted the result, partly because the number did not square with the prevailing belief in a normal total of 48 chromosomes, even if the cell was one *X* chromosome short.) In February 1956, Polani attempted to persuade a practiced cytogeneticist to help him; the man declined because he was unconvinced by Polani's arguments that the Turner's women might be *XO*. But in the fall of 1958, now eager to examine the karyotypes of Klinefelter's males, Polani turned with success to Charles Ford, whom he had met the year before at a conference on sex and the cell nucleus at King's College Hospital, in London.

Ford had recently perfected a method for treating bone marrow — another source of rapidly proliferating cells — in a way that yielded a large number of cells in a state of mitosis within a matter of hours. The method reduced to virtually nil a then-presumed risk of long-term tissue culture: that it could result in chromosomal changes of a misleading kind because they occurred not in the body but in the process of cell division in the culture itself. Early in 1958, Ford had used the bone-marrow technique to scrutinize a Klinefelter's karyotype in collaboration with Lazlo G. Lajtha, a hematologist at the Churchill Hospital, Oxford, and Patricia A. Jacobs, a young cytogeneticist from Edinburgh who had come to Harwell for a few months to learn the techniques of bone-marrow preparation. They had counted 46 chromosomes, including two *X*'s, which was consistent with the chromatin-positive reading characteristic of females. They had not found a *Y* chromosome. Even though the Klinefelter's was an apparent male, this was no surprise at the time. Fruit flies with an *XO* complement of sex chromosomes were males, while those with an *XXY* complement were females. The prevailing extrapolation from these data had it that the *Y* sex chromosome played no role in the determination of maleness, even in human beings. Still, the examination of one Klinefelter's karyotype hardly settled the matter, and late in 1958 Polani sent a sample of Klinefelter's bone marrow for analysis to Ford at Harwell.



Penrose determined in the 1930s that the incidence of Down's syndrome (represented here by the thick line) was a function of the mother's age. The dashed line plots total number of births (in thousands), and the thin solid line represents the number of babies born with Down's syndrome.

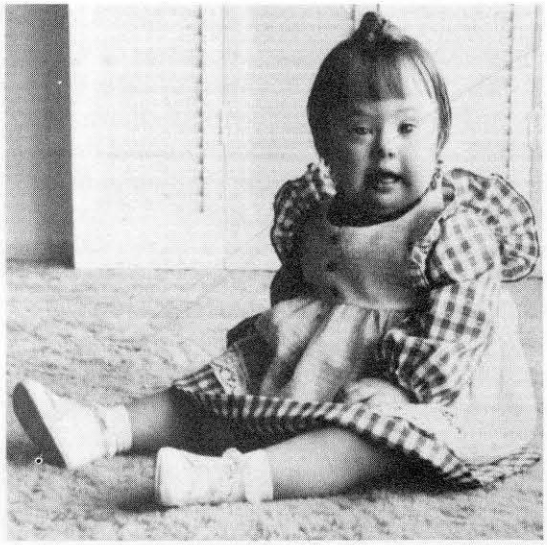
Unknown to Ford, the chromosomes of a Klinefelter's male had been under scrutiny in Edinburgh since the early summer by Patricia Jacobs and John A. Strong, a local physician. Jacobs had returned to her Medical Research Council Unit, which specialized in radiation genetics and where she had been examining the karyotypes of human beings with radiation-induced leukemias. Unable to find more than a few such people, Jacobs had decided to apply her newly mastered bone-marrow techniques in a resumption of the Klinefelter's work she had begun with Ford. Though she did not at first believe what the Klinefelter's karyotype revealed, Jacobs was compelled to the identical conclusion that Ford at Harwell, still ignorant of her investigations, reached when he scrutinized the sample from Polani: The Klinefelter's male karyotype contained not two but three sex chromosomes — two *X*'s plus the *Y* of the normal male. Jacobs and Strong published their results in January 1959. At the time, as Lionel Penrose later wrote to his long-time friend J. B. S. Haldane, the discovery of the extra Klinefelter's chromosome "astonished everyone." Not the least astonishing feature of the new knowledge was that human beings differed from fruit flies in the role played by their sex chromosomes: In *Homo sapiens*, the *Y* determined maleness, even if in *Drosophila* it did not.

The Klinefelter's results set Penrose to thinking about a subject that had long interested him — the disease then termed mongolian imbecility. The first systematic identification of the disease had been made in 1866 by the British physician John Langdon

Haydon Down. Down described a syndrome that, along with severe retardation, included an enlarged head and a prolonged, or epicanthic, fold to the eyelid; often there was also a fissured tongue and the so-called simian crease, a pronounced transverse palmar line. In Down's time, Western physicians had observed the syndrome only in Caucasians. Down supposed that the disease indicated a biological reversion in its victims to the Mongols of Asia, whom he thought they physically resembled, and who he assumed were a surviving example of an earlier human type. Down believed the disease to be congenital rather than hereditary, and he speculated that the reversion might be caused by parental tuberculosis.

The tubercular explanation was, of course, wrong, and so were others of a similar shot-in-the-dark nature advanced in the early 20th century. In the 1930s, Penrose demonstrated conclusively that the probability of the birth of a child with Down's syndrome depended strongly upon the age of the mother, with the probability rising rapidly after the age of 35. However, the physical cause of the disease still remained entirely unknown. Early in the 30s, the Dutch physician P. J. Waardenburg and the St. Louis pediatrician Adrien Bleyer independently suggested that Down's syndrome might be the product of a chromosomal anomaly, and by the end of the decade Penrose had come to embrace the suspicion. In 1952, at his urging, Ursula Mittwoch, a member of the Galton staff, scrutinized the sex-cell karyotype of a Down's male. Though inexperienced at cytology, she managed to count 24 chromosomes, half of the 48 that one would then expect to find in a normal cell after meiotic division — which implied that Down's syndrome was not the result of a chromosomal disorder. For Penrose, the Klinefelter's results reopened the question. Penrose knew of a Klinefelter's Down's at the Harperbury Hospital, identified in a search he had initiated there in the fall of 1958 for chromatin-positive males and chromatin-negative females. In his letter to Haldane a few months later, Penrose recounted, "Naturally, I wanted at once to try our luck with the Klinefelter mongol."

Charles Ford was ready and eager to do the karyotype analysis, but it took time to get the relatives' consent for the removal under anesthetic of the bone-marrow cells. Then, for three weeks or so from late February 1959, a virulent Asian flu epidemic com-



Characteristic of Down's syndrome are the eye folds that led early researchers to label the condition "Mongolism." (Photo courtesy of the Oregon Health Sciences University.)

pletely tied up the hospital facilities. In the meantime, reports filtered into England that Jérôme Lejeune, a young French human geneticist, had learned something of consequence about Down's syndrome karyotypes.

LEJEUNE'S CAREER IN genetics started in 1952, when, as a recent graduate in medicine, he returned from military service to work with Raymond Turpin at the Hospital Saint-Louis, in Paris. Turpin, a professor of pediatrics at the University of Paris, was one of the very few people in France at the time interested in human genetics. His hospital practice included a group of Down's syndrome patients, and he turned over responsibility for them to Lejeune. Neither Turpin nor Lejeune believed John Langdon Down's original hypothesis that victims of the condition were throwbacks to some atavistic Mongolian "race." In his clinical work, Lejeune saw a Down's child from Indochina whose appearance differed sharply from that of normal children of the region; the syndrome stood out among Orientals as well as among Caucasians. Lejeune suspected that Down's syndrome had something to do with hereditary mechanisms. Like a number of physicians elsewhere confronted with such inklings, he embarked on a postmedical course of study toward a doctorate in science with emphasis on biochemistry and genetics. Postwar French austerity made the task of research less straightforward: Lejeune had no laboratory, no microscope, only a single room without running water. Pondering what experimental research he might pursue under those conditions, he decided to concentrate on the palm prints of Down's victims.

In 1953, Lejeune scrutinized the configurations of lines on the palms of 93 Down's patients, 246 members of their families, and two large control groups drawn at random — except that one group was evenly divided for sex — from the Parisian population. Lejeune assessed the configurations quantitatively and arrived at a numerical index of the degree to which, on a given palm, they occurred in association with each other. He found that the Down's patients had a strikingly higher associative frequency of abnormal palm lines than did the people in either of the control groups. To Lejeune, this signified that Down's syndrome must involve some deep genetic change from the normal. Lejeune knew very little about primatology, but it occurred to him that a clue to the deep change might be found in the palm configurations of apes and monkeys — especially the lower-order monkeys from which the simian crease, that frequent palmar characteristic of the syndrome, took its name.

At the Natural History Museum in Paris, he measured the configuration of palm lines on the skins of the apes and monkeys preserved there. The palm lines of normal human beings showed no resemblance to those of either the lower-order monkeys or the anthropoid apes — orangutans, gorillas, and chimpanzees. But there were extraordinary similarities between the Down's palms and those of the inferior monkeys — for example, mangabeys and macaques. Lejeune supposed that the distinction between the palm lines of anthropoid apes and those of the lower-order monkeys must have resulted from the accumulation of numerous single-gene changes over evolutionary time. He speculated that the Down's palm lines, too, must arise from a polygenic difference between the Down's victims and normal human beings — occurring, obviously, not over evolutionary time but in one generation, from parent to child. Lejeune reasoned that the necessary change had to involve the only genetic material then known to be large enough to carry a polygenic message — a chromosome.

At this point, Lejeune's mind turned to the haplo-four fruit fly. (Cytogeneticists designate as "haploid" those cells — for example, mammalian gametes — that contain only half the normal number of chromosomes. The haplo-four takes its name from the fact that it possesses only one member of the fourth chromosomal pair found in normal *Drosophila.*) The haplo-four fruit fly has various abnormal characteristics, including thinner bristles, a shortened body, and a prolonged larval stage. No one of these characteristics announces the haplo-four; they declare themselves as an ensemble — a syndrome. Lejeune thought of the haplo-four as a kind of "mongol fly." Just as the "mongol fly" was missing a chromosome, Lejeune came to think, in 1954, that the victims of Down's syndrome must lack a chromosome, too.

Lejeune had by this time moved with Turpin's group to the Hospital Trousseau. He wanted to look at the chromosomes of his Down's patients, but he was not familiar with human cytogenetic techniques and was unable to find anyone in Paris who was. Besides, there was not much money for research and only limited laboratory facilities at the hospital. He therefore turned to various other subjects — mainly radiation genetics, for which Turpin, like many biologists, was able to raise funds in the mid-50s. All the while, however, he had his chromosomal hypothesis in mind and kept hoping to test it, especially after the work of Tjio and Levan was published.

The opportunity arose in 1957, with the arrival in Turpin's clinic of Marthe Gauthier, a cardiologist who had recently learned the technique of tissue culture; Turpin authorized her to use it in collaboration with Lejeune. Sometime about the spring of 1958, Gauthier cultured tissue taken from the fascia lata — the smooth connective tissue that covers muscle — of three Down's patients at the Hospital Trousseau. Lejeune, using the newly developed cytogenetic techniques, prepared karyotypes and examined them through a microscope discarded by the hospital's bacteriology laboratory; it was so worn that he had to stabilize its adjustment gears by inserting between them a piece of tinfoil from a candy wrapper. He photographed the karyotypes with equipment borrowed from the pathology department, expecting them to show, like those of the "mongol fly," the absence of a chromosome. Instead, they showed that the Down's patients had 47 chromosomes rather than the 46.

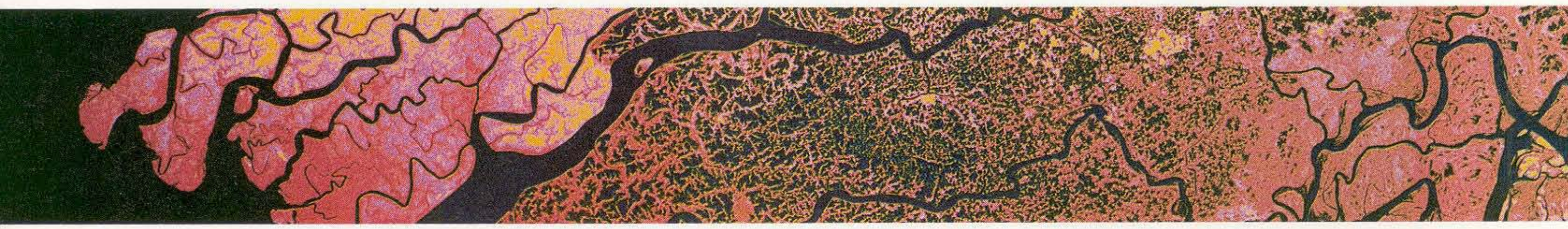
Lejeune wondered whether the extra chromosome was typical of the Down's patients or an artifact of the tissue culturing. Aging cultures were known to produce chromo-

continued on page 26

25 Years of Space Photography

Jet Propulsion Laboratory

California Institute of Technology

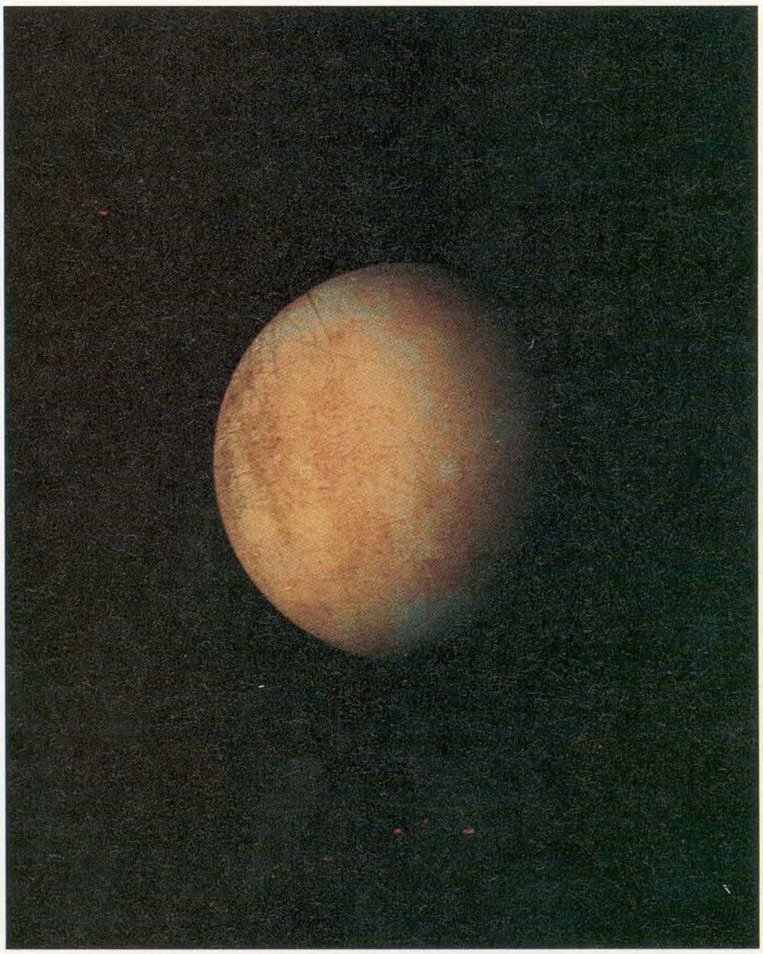


BAXTER ART GALLERY'S final exhibition celebrates a particularly appropriate theme for Caltech — the convergence of science and art. Organized by gallery director Jay Belloli, the show features nearly 140 images chronicling JPL's unmanned space exploration — from the early Ranger and Surveyor lunar missions, the Mariners (Mars, Venus, and Mercury), the Viking orbiters and landers (Mars), to the recent Voyagers (Jupiter and Saturn). Earth is also represented, seen by the radar of Seasat and the two space shuttle experiments of the Shuttle Imaging Radar (SIR-A and SIR-B). And the Infrared Astronomical Satellite (IRAS) contributes shots of its penetrating glimpses outside the solar system into our own galaxy and beyond.

Many of the spectacular photographs, which were made by JPL for NASA, have not been widely published, but some of the pictures will be familiar to all who watched their television screens in wonder as spacecraft cameras brought new worlds into close view — the barren surfaces of the Moon and Mars, Jupiter's swirling clouds and Great Red Spot, and Saturn's rings. At the time, admiration of the beauty of these pictures was equaled by awe at the technology that conveyed them; the emphasis of the current show, however, lies on the images themselves as art. As Los Angeles art critic Christopher Knight writes in the show's catalog, ". . .framed and hanging on the walls of a gallery, space photographs are radically re-contextualized: they are

Above: The Ganges floodplain (Bangladesh) — by SIR-B, 1984

Below: Europa — by Voyager 2, 1979

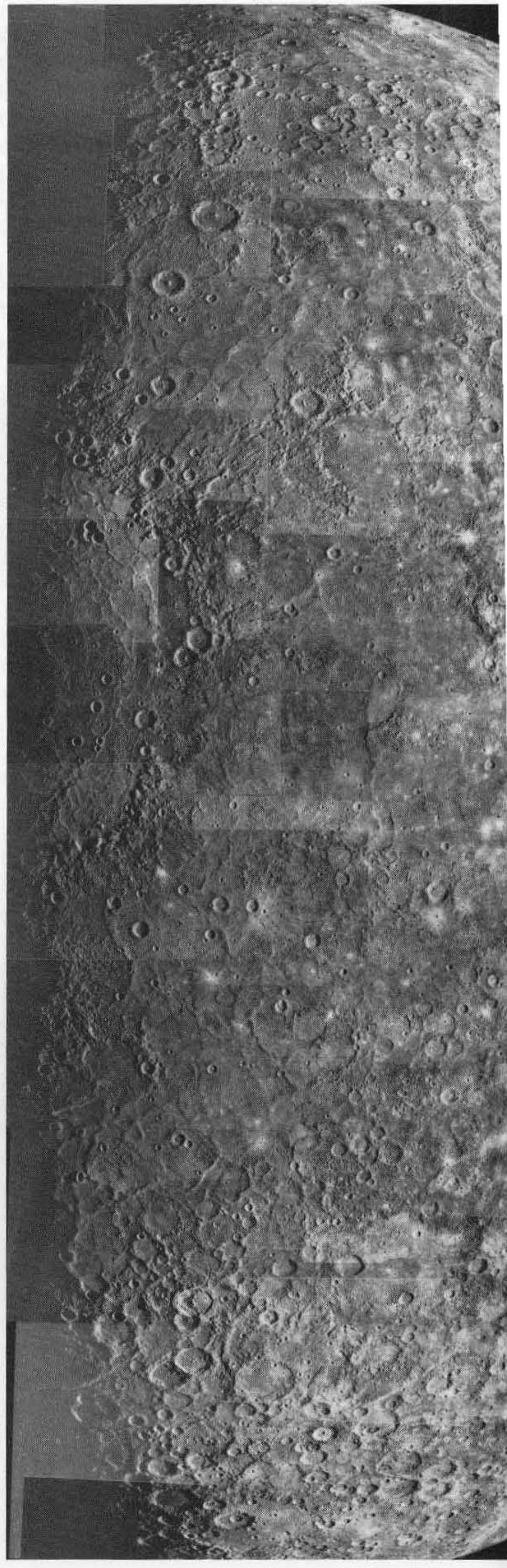


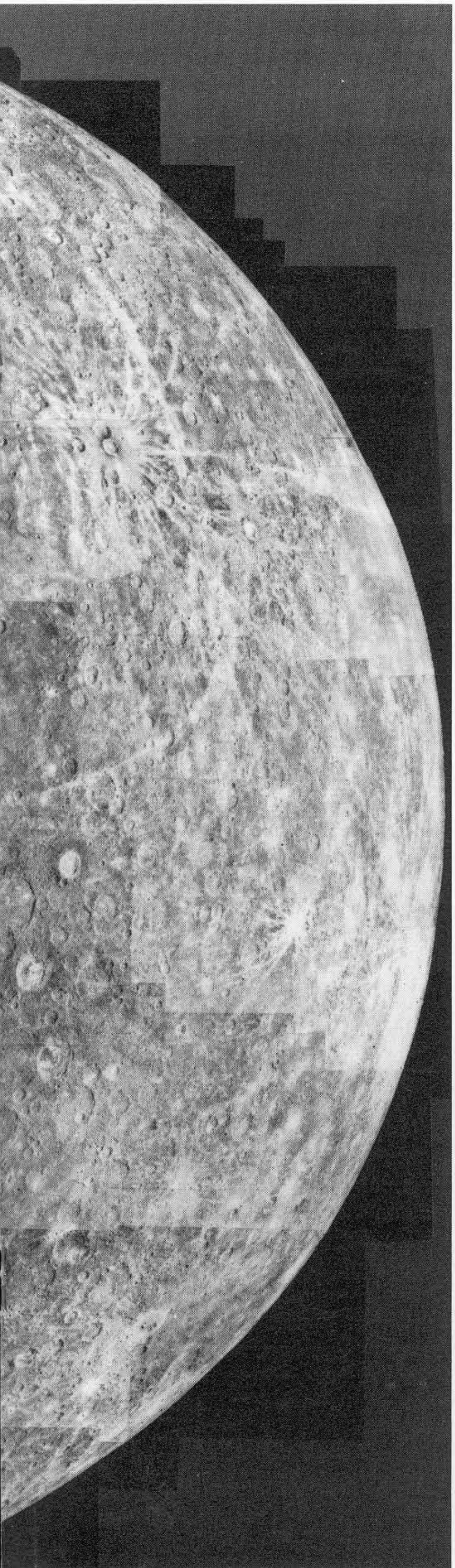
transformed from offerings of visual evidence into aesthetic objects for examination."

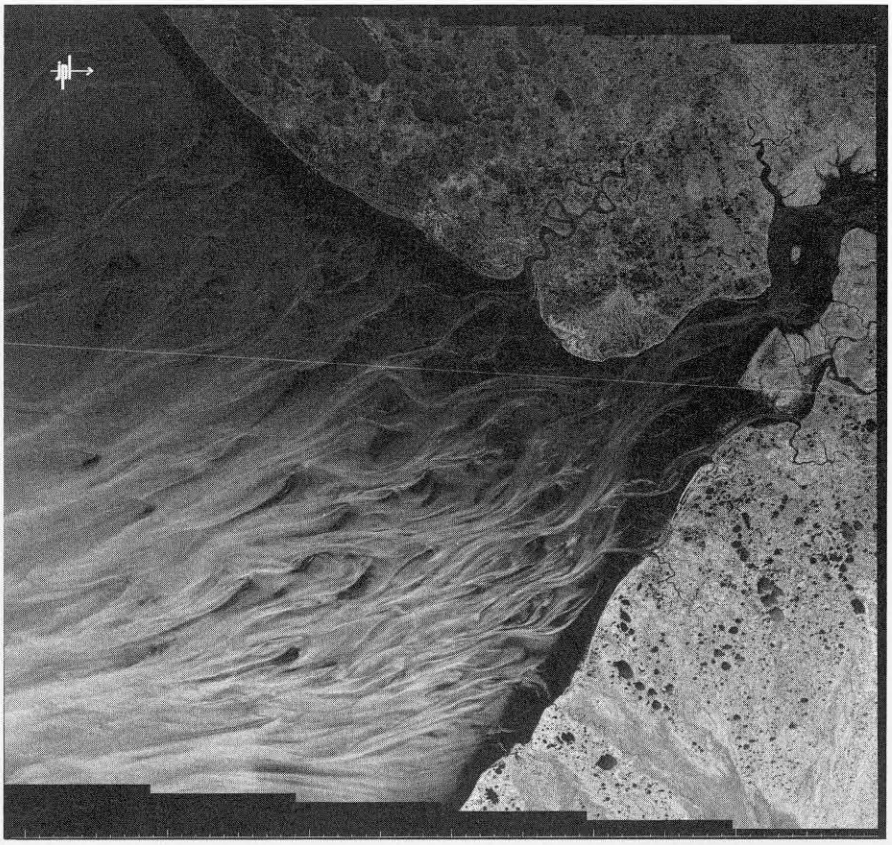
In his catalog introduction, Belloli suggests that "Marcel Duchamp's life-long meditation on the role of the determination of what constitutes art. . .and the participation of both the maker and the viewer in that decision — is inescapable as one looks at these images." He goes on to note that "these photographs are often created with a large number of what are, in fact, artistic decisions." Knight also stresses the scientist-as-artist in linking the JPL missions with the tradition of 19th-century photographers who charted America's wilderness: "The singular and independent photographer is here replaced by the diverse and interdependent multitude of scientists and technicians whose coordinated commands, responses, and actions set into motion a complex chain of events that results in a photographic image."

The exhibition, which was funded by a grant from IBM Corporation, runs from May 22 to July 31. It will then travel to the IBM Gallery of Science and Art in New York for a November opening. W.W. Norton & Company, Inc., will distribute the catalog. □

Ganymede — by Voyager 1, 1979



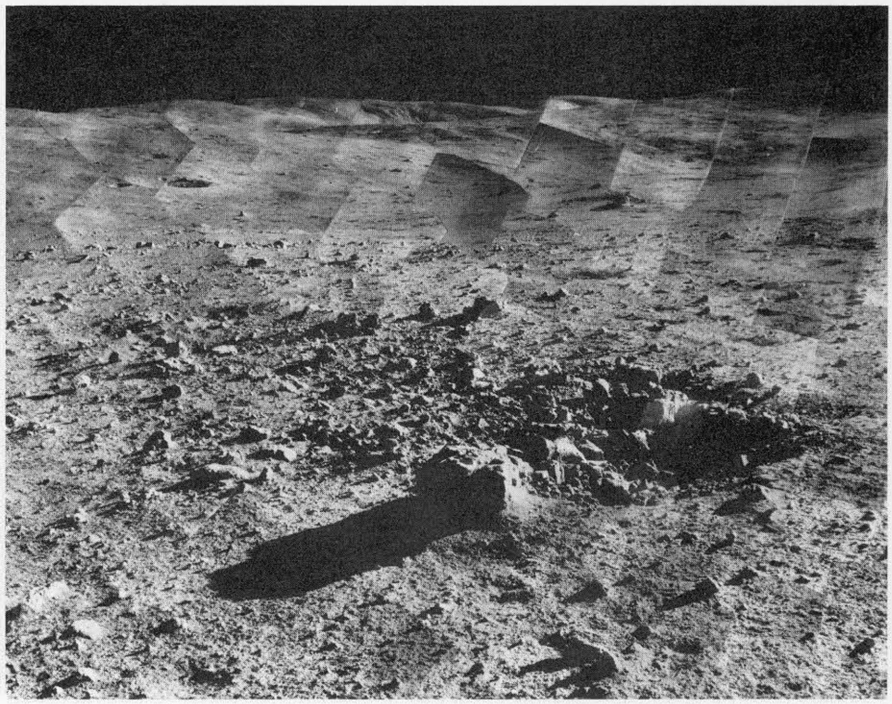


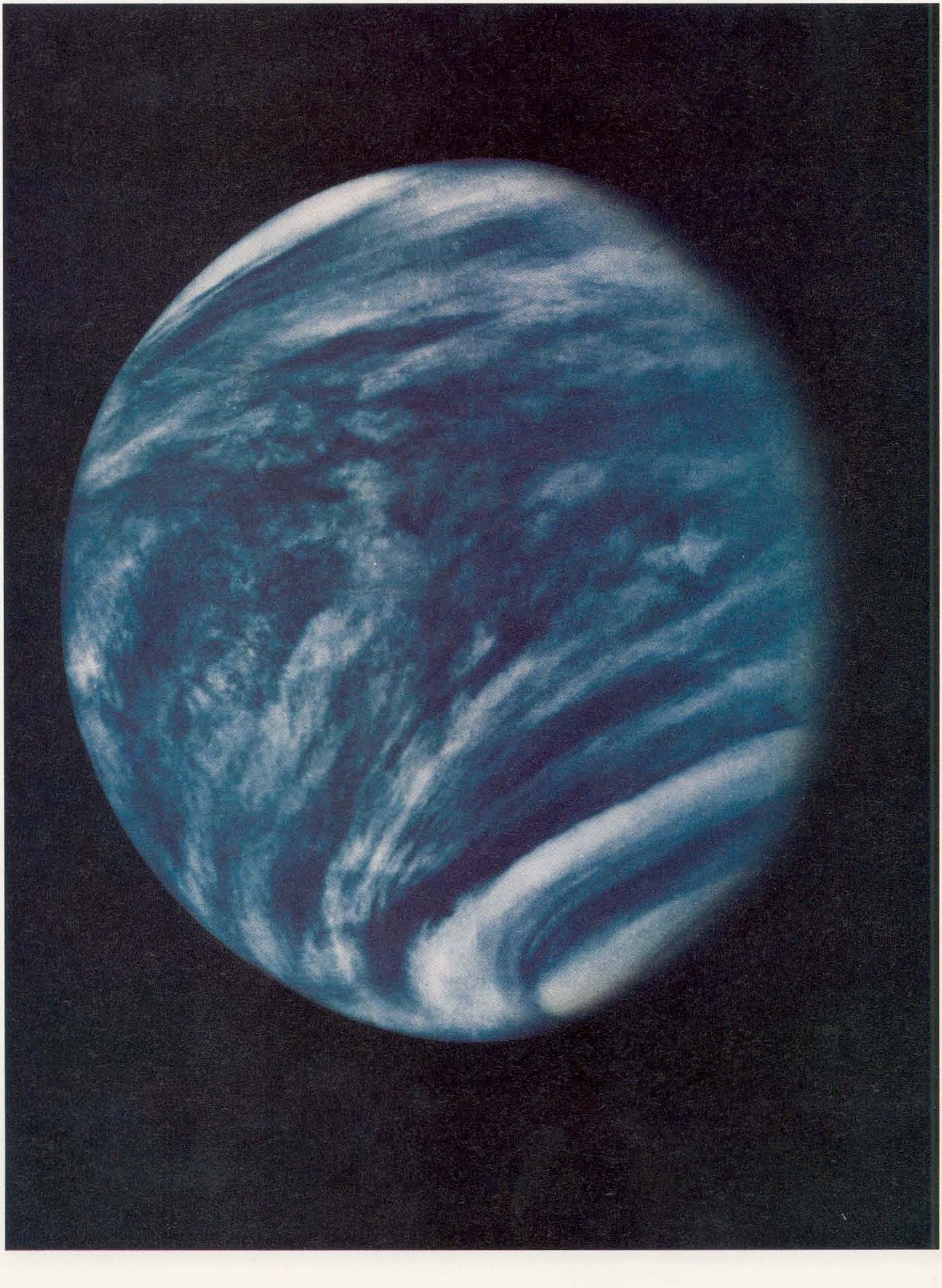


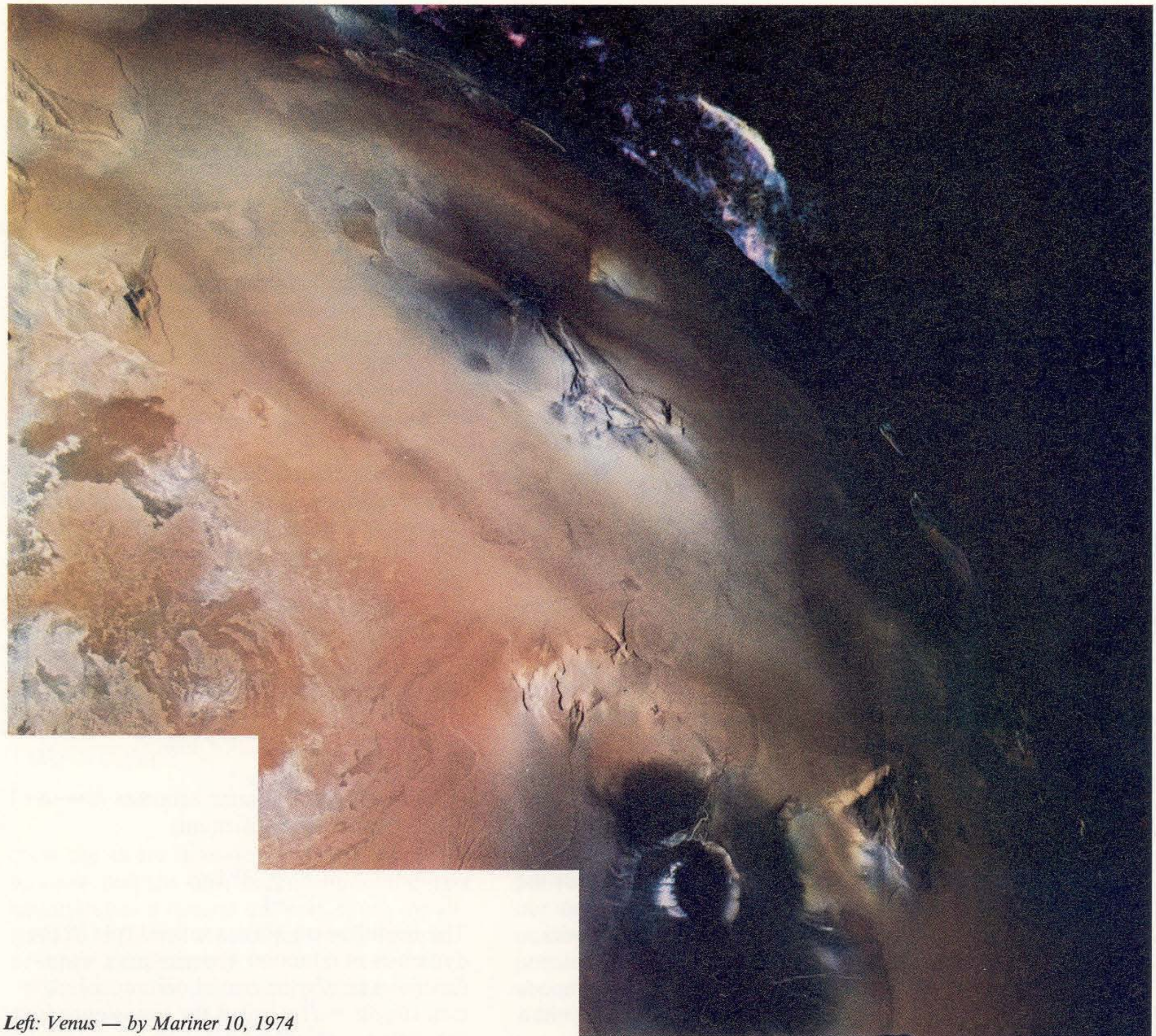
***K**uskokwim River (Alaska) — by Seasat, 1978*

Left: Mercury — by Mariner 10, 1974-75

Near the Crater Tycho, Moon — by Surveyor VII, 1968

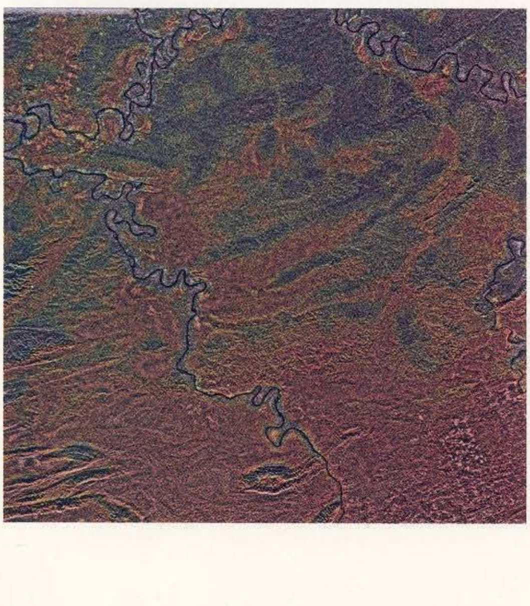






Left: Venus — by Mariner 10, 1974

Above: Io (with geyser plume Pele) — by Voyager 1, 1979



Left: Southern Mexico and Guatemala — by Seasat 1978

The Theory of Schrödinger Operators: What's It All About?

by Barry Simon

CALTECH HAS BECOME a world center of the study of Schrödinger operators. What is the theory of Schrödinger operators anyway? In short, it is the rigorous mathematical study of the Hamiltonian operators of nonrelativistic quantum mechanics.

Schrödinger operators are a part of mathematical physics, an area that suffers the usual fate of interdisciplinary areas: Too often the mathematicians think it's physics, and the physicists think it's mathematics. (Chemical physics has the same problem. Many years ago so did biochemistry, but in a sense it succeeded in absorbing a large part of biology.) Perhaps the reader will appreciate that Schrödinger operators have useful insights to offer to both mathematics and physics.

In quantum theory, a fundamental role is played by the energy written as a function of the momentum and position of the constituent particles, but with the twist characteristic of quantum mechanics (due to the Heisenberg relations $[p,x]=-i\hbar$ that the momentum, p_j, is replaced by the elementary differential operator $-i\hbar\ \partial/\partial x_j$ (where $\hbar$ is the rationalized Planck's constant, $h/2\pi$; having been careful to put $\hbar$ here, for typographic simplicity I henceforth will use units with $\hbar = 1$ and with electron mass equal to ½). Thus, for a classical system of N electrons with momenta p_j ($j=1,\ldots,m=3N$ for the N 3-vector momenta) and classical energy

$$\sum_{j=1}^{m} p_j^2 + V(x),$$

the Hamiltonian operator becomes $H=-\Delta+V$ where the Laplacian Δ equals

$$\sum_{j=1}^{m} \partial^2/\partial x_j^2.$$

The Hamiltonian plays a crucial role in the dynamics of quantum systems since wave functions satisfy the partial differential equation $i\partial\psi/\partial t = H\psi$ called the time-dependent *Schrödinger equation.*

In physics textbooks, H is called the Hamiltonian since it is the quantum analog of the object introduced in classical mechanics by William Hamilton. The same name is also used for the quantum energy operator of relativistic quantum field theory. To emphasize that one is looking only at the nonrelativistic case, the Hamiltonians of nonrelativistic quantum mechanics are called Schrödinger operators. This honors Erwin Schrödinger, one of the founding fathers of quantum mechanics. Thus the theory of Schrödinger operators is simply the study of the differential operators $-\Delta+V$.

At first sight, one would not think that such an innocent-looking object could have a very interesting structure. Of course, one might conclude the same thing about the classical analog, $m\ddot{x} = -\nabla V$, which is rich enough to describe phenomena as varied as the dynamics of binary stars or of water in a waterfall. In the same way, Schrödinger operators describe the full richness of quantum dynamics. Although there are results involving general V (perhaps there has been too much work on the general and not enough on the specific classes), much of the recent thrust has focused on the Vs relevant for atomic and molecular physics, the description of perfect solids, and more exotic objects such as amorphous materials and quasicrystals. Here I will describe several results, all related to atomic physics, which I hope will give a flavor of the scope and significance of the field.

The first question that a mathematician might ask concerns the existence of solutions of the time-dependent Schrödinger equation $i\dot{\psi}_t = H_t$. For some reasonable class of Vs, including that describing N electrons moving in the Coulomb field of M protons (taken infinitely massive) in fixed positions $\vec{R}_1, \ldots, \vec{R}_M$ (equation 1)

$$V(\vec{x}_1, \ldots, \vec{x}_N) = -\sum_{\substack{1 \leqslant i \leqslant N \\ 1 \leqslant j \leqslant M}} \left|\vec{x}_i - \vec{R}_j\right|^{-1} + \sum_{1 \leqslant i < j \leqslant N} \left|\vec{x}_i - \vec{x}_j\right|^{-1} + \sum_{1 \leqslant i < j \leqslant M} \left|\vec{R}_i - \vec{R}_j\right|$$

(now the xs are three-vectors), one would like to know that the time-dependent Schrödinger equation has a unique solution, if not for all initial conditions, at least for a very large set of initial conditions.

Formally, the solution is given by

$$\psi_t = exp(-itH)\psi_0,$$

but what does $exp(-itH)$ mean? Expanding the exponential and considering terms like $\Delta^2 V \psi_0$, where the derivatives of V produce non-square integrable singularities, will show the problem with a naive approach. On a slightly more sophisticated level, students of quantum mechanics learn that they cannot study the quantum motion of a particle in a box without specifying boundary conditions. How does one know that boundary conditions are not needed at infinity or at the Coulomb singularities in solving the Schrödinger equation with potential (1)?

There is one attitude about these questions that needs to be addressed — that is, that you don't need existence proofs for a physical theory because nature is an existence proof. This idea of nature as a grand analog computer misses the whole point of existence proofs: We are not testing nature but rather our theories, which could, after all, be wrong or incomplete. A paradigm of this phenomenon concerns the changing attitude about quantum electrodynamics (QED). After the formulations of the theory by Feynman and Schwinger in the 1940s, a common attitude was that the impressive agreement with experiment proved that the theory had to be consistent. The current opinion among elementary particle theorists is quite different: As an abelian gauge theory, QED is most likely mathematically inconsistent. Rather, high energy physicists hope that the non-abelian gauge theory associated to the unified treatment of electromagnetic and weak interactions is consistent. The agreement with experiment is because the formal perturbation expansion of the putatively inconsistent theory is quite close to that of the putatively consistent theory.

In response to the development of the new quantum mechanics (1925-28), John von Neumann developed a theory of unbounded operators in Hilbert space precisely to deal with foundational questions in quantum mechanics. What von Neumann realized is that the key to solving the time-dependent Schrödinger equation was the proof that H has a abstruse mathematical property called essential selfadjointness.

But here progress on this particular problem stalled for 25 years, in part because von Neumann was convinced that the problem of proving essential selfadjointness of $-\Delta + V$ for V of the form (1) was an impossibly hard problem. And he was not shy about informing others of his opinion. Indeed, I am told that as late as 1950, he insisted that the problem was not trivial even for the hydrogen atom. (Of course, physicists do know how to write down all the eigenfunctions, including continuum eigenfunctions, in this case; in fact, by using the rotational symmetry of the hydrogen atom, one can reduce this case to some ordinary differential equations where selfadjointness was completely analyzed by Hermann Weyl in 1912. Using his methods it is not hard to prove essential selfadjointness for the hydrogen atom Hamiltonian.) This is ironic, because the two main inputs that turn out to be essential for the proof of this fundamental property are an abstract result in operator perturbation theory proven by Franz Rellich in Germany in the mid-1930s and certain inequalities now known as Sobolev inequalities, developed in the 1930s by Sergei Sobolev in the Soviet Union and Salomon Bochner in the United States, among others. These tools were available by 1936 or so. But nobody put them together, perhaps because of von Neumann's well-known attitude that the problem was too hard to work on.

The essential selfadjointness of atomic Hamiltonians was established by Tosio Kato (since the late 1950s professor of mathematics at UC Berkeley). Here is his description of the history of his work, taken from his acceptance speech for the Wiener Prize (which appeared in the November 1980 issue of the *Notices of the American Mathematical Society*):

"During World War II, I was working, in the countryside of Japan, on the spectral theory of Schrödinger operators and perturbation theory. As a physics student I had been led to study these problems on my own, since no one seemed to pay attention to them in spite of the existence of the general principle given by von Neumann. My first efforts were directed toward establishing the essential selfadjointness of Schrödinger operators and laying a mathematical foundation for perturbation theory. (At that time I did not know of Rellich's work.)

"These works were more or less completed by the end of the war, but I was not very lucky with their publication. A couple of years later I submitted two papers on the subject to *Physical Review*. They were soon forwarded to the *Transactions of the American Mathematical Society*, where the manuscripts were passed from one referee to another without success, eventually to be lost. I had to resubmit new manuscripts. After three years from initial submission, the papers were finally saved by the last referee."

Interestingly, the analog of Kato's theorem for classical mechanics is open. That is, one can ask about global (in time) solutions of Newton's equations for point masses interacting gravitationally (or electrostatically). Even in the two-body case, global solutions will not exist for *all* initial conditions, since collisions are possible in finite time. But in the two-body case, only initial conditions with zero angular momentum can have collisions, so for almost all initial conditions, the classical two-body problem has global solutions. The analog of this was proven for the three-body problem by George Birkhoff (using results of Painleve and Sundman) in 1927, and for the four-body problem by Donald Saari (Northwestern) in 1977. It is open for $N \geqslant 5$ where there are indications of a new phenomenon: initial conditions where particles travel infinitely far in finite time (the infinitely large velocities are possible because of pairs spiraling into each other). It is not clear whether these only occur for a set of initial conditions of measure zero. The quantum result can be viewed as an indication that for general N, the classical problem does have solutions for most initial conditions. The reason that quantum mechanics is nicer than classical mechanics is the uncertainty principle, in this case expressed through the Sobolev inequalities.

Kato's work can be viewed as the birth of the modern theory of Schrödinger operators. Once we know this fundamental result, we can begin to ask many detailed questions. Some of the most subtle involve an area I call "quantum potential theory," which is the rigorous study of exact Coulomb binding energies in quantum mechanics.

A basic result in quantum potential theory is "the stability of matter." This involves a problem first raised by Lars Onsager (known for his work on the Ising model, and on nonequilibrium thermodynamics, for which he received the Nobel Prize in chemistry) in the 1930s. It is a basic fact of astrophysics that bulk matter in the absence of nuclear effects undergoes gravitational collapse. Onsager asked how we know that bulk matter doesn't undergo "electrostatic collapse." We know that quantum mechanics yields stability of a system of one electron and one proton. In classical mechanics the electron would fall into the proton, but in quantum theory this doesn't happen. This implies that a system of 10^{26} protons and 10^{26} electrons won't collapse to zero size, but it certainly isn't obvious *a priori* that such an array won't collapse to a very small size indeed. Of course, since individual electrostatic forces are much stronger than gravitational, if there were electrostatic collapse, it would require much less matter than gravitational collapse, so we would observe it. Since we don't, it must not occur, but this doesn't explain *why* it doesn't occur and whether the fact that it doesn't occur is just due to quantum mechanics and electrostatics.

The realization came quite early that lack of collapse is implied by the binding energy of a large system of particles being an extensive quantity, that is, that a system with potential (1) has a total energy bounded from below by $-c(N+M)$ for some constant, c. Freeman Dyson (Institute for Advanced Study) and Andrew Lenard (Indiana University) first proved that this is the case in 1967. There is one especially striking aspect of their work: It is critical for their proof that electrons are fermions, that is, that they obey the Pauli exclusion principle. And we know now that this is essential; if both electrons and protons were bosons, electrostatic collapse would take place. While the precise rate of collapse is not known, it is likely that in the neutral $(N=M)$ case, volume shrinks as the inverse fifth root of N. A system of 10^{26} "Bose" electrons and protons would live in a volume a very small fraction of a single hydrogen atom.

The relevance of the Pauli principle, even for qualitative features, is ubiquitous in quantum potential theory. For example, last year Elliott Lieb (Princeton), Israel M. Sigal (UC Irvine), Walter Thirring (University of Vienna), and I showed that the number of electrons, $N(Z)$, that one can bind to a charge Z nucleus grows as Z in the sense that $N(Z)/Z$ goes to 1. But if electrons were bosons, Lieb and Raphael Benguria (University of Chile) showed that the analog $N_b(Z)$ grows at least as fast as $1{\cdot}21Z$. The observed fact of nature that there seem to be no negative ions with net charge larger than 1 is critically dependent on the Pauli principle.

As realized by Lieb and Joel Lebowitz (Rutgers), an important consequence of the Dyson-Lenard theorem combined with a study of shielding is the existence of thermodynamics for bulk matter, that is, of the extensive nature of basic quantities such as pressure in the quantum statistical mechanics of Coulomb systems.

The Dyson-Lenard result is not the end of the story, because the constant c in their bound on the energy is roughly 10^{14} Rydbergs (a Rydberg is the binding energy of hydrogen). Thus, while matter cannot shrink indefinitely, it could shrink so that interparticle distances were roughly 10^{-14} Bohr radii and still not violate the theorem of Dyson-Lenard. The large number 10^{14} in their proof occurs in part because of complexity. Sacrificing some truth to humor, one could say that their proof has 14 steps, each of which introduces a factor of 10 error. Dramatic progress was made by Lieb and Thirring in 1975, who (counting some later refinements of their ideas) obtain a constant of roughly 20 Rydbergs.

The physics behind the Lieb-Thirring proof is quite illuminating; it is perhaps worth describing a part of it. There is an old, quasiclassical approximation to quantum mechanics called the Thomas-Fermi (TF) approximation. In 1973 Lieb and I rigorously proved that this approximation is exact in the large Z limit in the sense that it properly describes the total binding energy and the electron density of the core. It does not correctly describe electrons near the outer shell, nor the ionization energies relevant to chemistry. Quantum chemists in the 1950s tried to compute numerically molecular binding energies using the TF approximation and were unable to find any binding. In response to this, Edward Teller proved in 1960 that molecules never bind in TF theory. (Lieb and I later supplied some points of mathematical rigor, especially the existence of solutions of the TF equation, but Teller's argument is quite close to the rigorous one.) Thus, stability of matter is easy in TF theory: By Teller's result, the energy of an array of protons and electrons is always bounded from below by the total binding energy of well-isolated protons and an appropriate number of electrons. Since it can be shown that in TF theory a proton binds only one negative charge, in TF theory the binding energy of N protons and M electrons is bounded by cN, where c is the binding energy of hydrogen in the TF approximation.

Lieb and Thirring prove this by using their extension of the Sobolev inequalities (the Pauli principle enters in this step) and an additional trick that the total quantum energy of a system of N protons and M electrons is bounded below by $-dM+TF'$, where d is a constant related to c and TF' is the TF energy, but in a theory with the wrong value of h. Thus the bound

$$TF' > -c'N$$

implies stability of matter.

In a real sense, their proof has the right physics behind it. Stability is a statement of lack of collapse. This collapse is prevented by the interaction of "atomic cores," and Teller's theorem is precisely an assertion that cores (which, in the large Z limit, are described by TF theory) repel. Of course, $Z = 1$ is not large Z, so that it isn't clear that TF theory will apply here; Lieb and Thirring's discovery is that, if one is willing to make a small sacrifice in constants, it does apply.

The last example I will discuss is slightly more technical in detail. Among other things, it illustrates that in mining for pyrite, you can occasionally discover gold. Simple-minded, two-body scattering theory breaks down precisely at Coulomb potentials. There is a logarithmic infinity that must be handled. From a time-dependent point of view, this was done in 1964 by John Dollard (University of Texas). But, typically, mathematicians are not satisfied with treating only the physically relevant case, but want to understand where the modified scattering theory breaks down, so literature has developed on scattering for potentials decaying more slowly than Coulomb. I must confess that, while I recognize the validity of this area, I have not found it especially attractive or interesting. When I was starting out in the early 1970s, two other bright, young mathematical physicists, Rick Lavine (University of Rochester) and Jean Michel Combes (University of Toulon), separately proposed studying long-range scattering using a mathematical discipline called C*-algebras. Not only was the problem of limited interest, but I was convinced that this was the wrong approach to the problem. So, being a brash young man at the time, I didn't hesitate to tell both Lavine and Combes that they were wasting their time. In a sense my opinion was correct: The C*-algebra approach to the problem has not gotten very far, and there are now much better ways of analyzing the problem. But fortunately Lavine and Combes didn't listen to me, because each of them ran into technical problems that forced them to develop striking new methods. Lavine's ideas were a major element in a key breakthrough by Eric Mourre (CNRS Marseilles) in 1979. Interestingly enough, while the methods of Lavine and Combes seem to be unrelated, recent work by Peter Perry, the Bantrell Research Fellow in Mathematical Physics here at Caltech (with Arne Jensen at the University of Kentucky and Mourre) has shown an intimate relation between Mourre's descendent of Lavine's ideas and the Combes idea.

Combes's ideas originally appeared as an appendix to a paper on the C*-approach to long-range scattering. After some reflection, Combes decided to perform an appendectomy and throw the patient away — his paper never appeared, but he pursued the appendix. In 1971 Combes published two papers developing this approach: one with Jean Aguilar (CNRS Marseilles) on the two-body case, and one with Eric Balslev (University of Arhus) on the more subtle multiple-particle case. The main result of this analysis was a proof of the non-occurrence of a mathematical pathology called singular continuous spectrum in atomic and some other multiparticle quantum systems. Shortly thereafter, in several papers, I exploited the method to study resonances and, in particular, the mechanism whereby an embedded bound state turns into a resonance. Then quantum chemists and calculational atomic physicists, led by John Nutall (University of Western Ontario), got interested in the method as a practical way of computing resonances from first principles. Some of the significant work on molecular resonance was done by Bill McCurdy, now at Ohio State, and Tom Resignio, now at Lawrence Berkeley Laboratory, who learned the method while working (as graduate student and postdoc respectively) in Professor of Theoretical Chemistry Vince McKoy's group here at Caltech.

As we shall see, the group of dilations continued analytically plays a critical role in the Aguilar-Balslev-Combes theory. Combes, being French, dubbed the method "dilatation analyticity," later shortened to "dilation analyticity." The atomic physicists and quantum chemists, not liking fancypants language, called the method "complex scaling," the most common name now.

We begin by describing the idea for the case of the hydrogen Hamiltonian,

$$H = -\Delta - |r|^{-1},$$

whose spectrum has a continuous part

$$[0,\infty),$$

and a discrete part, the eigenvalues at

$$-\frac{1}{4}n^{-2}\ (n=1,2...).$$

Under the scale transformation

$$r \rightarrow e^{\theta}r,$$

H goes into

$$H(\theta) = -e^{-2\theta}\Delta - e^{-\theta}|r|^{-1}.$$

This operator has a natural analytic continuation to complex

$$\theta = \varphi + i\eta\ (\varphi,\eta\ \mathit{real}).$$

What is the spectrum of $H(\theta)$? The continuous spectrum should come from states near infinity where $|r|^{-1}$ doesn't count; that is, the continuous spectrum should be that of

$$-e^{-2(\varphi+i\eta)}\Delta$$

(this can be made precise by a theorem of Weyl). Since this operator is just a multiple of $-\Delta$, its spectrum is just

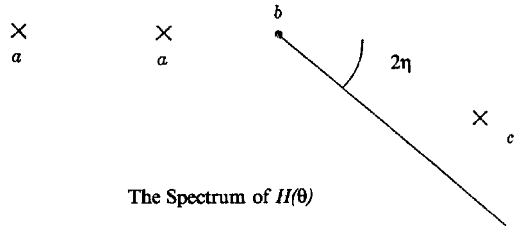
$$\{e^{-2(\theta+i\eta)}\alpha|\alpha\ in\ [0,\infty)\} = \{e^{-2i\eta}\alpha|\alpha\ in\ [0,\infty)\}.$$

Thus, as η varies, the continuous spectrum moves away from the real axis. However, a separate argument shows that the discrete eigenvalues

$$-\frac{1}{4}n^{-2}$$

don't move. As the continuous spectrum swings down, new eigenvalues can appear, but only out of the continuous spectrum. Put differently, if $\eta>0$ is decreased to 0, any eigenvalue of $H(\theta)$ persists, except that if the continuous spectrum hits them, they can be gobbled up and disappear (the Pac Man theory of resonances??). Clearly, one should associate these new eigenvalues with resonances. Such eigenvalues do not occur for the hydrogen Hamiltonian, but for multiparticle Coulomb Hamiltonians there is a similar theory: $H=T+V$, the kinetic and Coulomb energy

$$H(\theta) = e^{-2\theta}T + e^{-\theta}V.$$



The Spectrum of $H(\theta)$

(a) Discrete eigenvalues of H

(b) Thresholds of H

(c) Resonance eigenvalues

Now the continuous spectrum is in various rays,

$$\{t+e^{-2i\eta}\ \alpha|\alpha\ in\ [0,\infty)\}$$

where t is a possible scattering threshold of the system. Eigenvalues of $H(\theta)$ do occur and can be computed accurately by variational methods. Moreover, this precise mathematical definition of resonance allows the rigorous study of a wide variety of objects. For example, I was able to prove the convergence of time-dependent perturbation for Auger states, and Evans Harrell (Georgia Tech) and I, using the extension of the theory to Stark Hamiltonians (due to Ira Herbst of the University of Virginia), were able to make the Oppenheimer-Lanczos formula for the leading asymptotics of Stark resonances in hydrogen a mathematical theorem.

What then does the theory of Schrödinger operators accomplish? There is an occasional contribution to other parts of physics, especially in areas such as the theory of resonances or the theory of random impurities, where there are mathematical subtleties with real physical significance. Also, there are important spinoffs to mathematics. To name two areas, operator theory, especially spectral analysis, and the theory of path integrals have been illuminated in significant ways during the recent past by the theory of Schrödinger operators. But in the end, there is the internal dynamic connected with intellectual honesty — precisely what can and what cannot be explained rigorously from first principles, starting with the basic formalism of nonrelativistic quantum mechanics? There results a theory of great beauty with intimate connection to a wide variety of aspects of both mathematics and theoretical physics. □

Human Chromosomes

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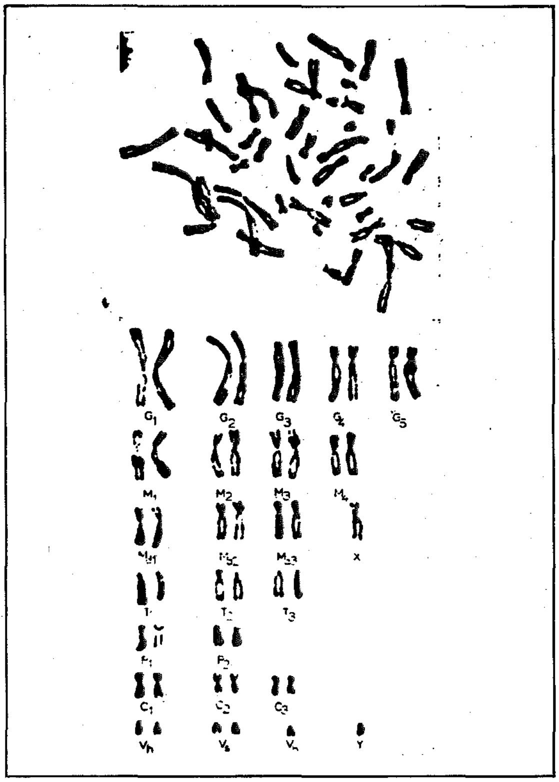
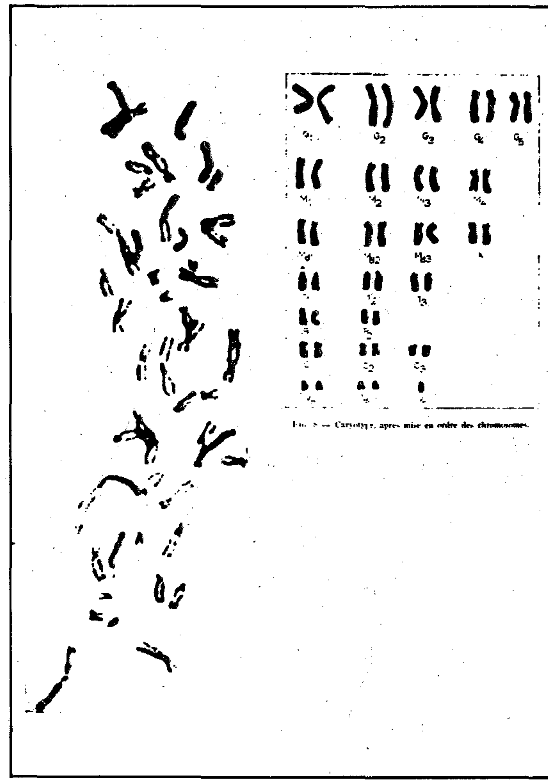




Published in 1959, two of Lejeune's Down's karyotypes (before and after ordering) show the extra chromosome in both the male (left) and female.

somal anomalies. But the cultures had been no more than a month old before he obtained the karyotypes — too short a time, Lejeune thought, for the aging phenomenon to occur. More troubling to him was a recent paper by Masuo Kodani, an American cytogeneticist then working with the Atomic Bomb Casualty Commission in Japan, claiming that in some normal human beings the chromosome number might be 47. If Kodani was correct, then the "extra" chromosome Lejeune had detected in his patients might not be extra at all and might have nothing to do with Down's syndrome. In a lecture at McGill University in September 1958, just after the Tenth International Congress of Genetics, in Montreal, Lejeune swallowed his doubts enough to show the photographs of the three Down's karyotypes and advance his belief that the cause of the syndrome was an extra chromosome. His audience seemed for the most part unconvinced.

After he returned to Paris, Lejeune prepared karyotypes of cells from eight non-Down's patients at the Hospital Trousseau. Each of the karyotypes showed 46 chromosomes. Though still somewhat anxious about putting his Down's results into print, he finally published the work in the *Comptes Rendus* of the French Academy of Sciences in January 1959. In the same journal, in mid-March, he reported the results of an examination of nine Down's karyotypes and argued with greater confidence that the extra chromosome was the cause of the syndrome.

In England by now, the crowding of Harperbury Hospital had eased enough to take the bone-marrow sample from the Klinefelter's Down's (Orlando J. Miller, a young Amercian physician then on a Population Council fellowship at the Galton Laboratory, dates the event between March 19 and March 23, 1959.) Half the sample was sent to Ford at Harwell, who recalls finding the extra Down's chromosome (plus, of course, the extra *X* for the Klinefelter's character) just two days after hearing about Lejeune's results. At the Galton, Miller and Ursula Mittwoch detected the identical chromosomal anomaly in their half of the bone-marrow sample. Additional confirmation came from Edinburgh, where Jacobs and her co-workers, also without knowing about Lejeune, had begun to look at the chromosomes of Down's victims because they tended to suffer from a high incidence of leukemia. News of the Down's results moved the provost at University College London in May to send Penrose a note: "It must be one of the most important things that has happened in genetical studies for a long time." And it was. Penrose remarked some months later that the events of the past year amounted to "a major breakthrough in the science of human genetics," adding that he found "the photograph of the cell from the man with two extra chromosomes from which the intelligence level, the behavior and sexual characters can be confidently predicted, just about as astonishing as a photograph of the back of the moon."

However, there was still doubt about the nature of the extra Down's chromosome. Penrose thought that it was a member of a trisomy — that is, the occurrence of one of the 22 autosomal chromosomes as a triplet rather than as a pair. Lejeune had not been certain — and neither had the other investigators — whether it was that or a supernumerary chromosomal piece of unknown origin. But within a year the abnormality was demonstrated to be indeed a trisomy — of the chromosome designated No. 21 by agreement at a genetics conference in Denver, Colorado, in April 1960. (The agreement assigned numbers to the chromosomes in order of descending size.)

Also in 1960, investigators in Sweden, in addition to Polani and Ford, and Penrose and others in England, concluded that a particular form of this trisomy accounted for the small number of cases of familial occurrence of Down's syndrome. It arose from the presence in some people of what is called a translocation — in this case, the attachment of one of the 21-chromosomes to the 14-chromosome. If a gamete containing the 14-21 combination plus the other 21-chromosome was passed on to a fetus, the offspring would possess two regular 21-chromosomes plus the 21 on the No. 14. If a gamete transmitted the 21- and 14-chromosomes only in their hybrid form, the child would be normal. But because these chromosomes were attached to each other the child would be a carrier, and his or her children would be at risk for trisomy-21. The detection of the cause of "mongolism" in such cellular accidents finished off — or should have — its vestigial association with some kind of atavism. Lejeune, Penrose, and others publicly urged that the racially tinged nomenclature of the condition be abandoned in favor of different terms, including "Down's syndrome" or "trisomy-21."

The sharp turn of events in human cytogenetics originated in different approaches — particularly in the Cartesian rationalism of Lejeune on the one side of the Channel and British step-by-step empiricism on the other, but they joined incandescently to light up a vast unexplored region on the human cytogenetic map. Charles Ford had analyzed a Turner's bone-marrow sample sent him by Polani and had reported in 1959 that, as Polani suspected, Turner's females were missing a second sex-chromosome. In 1960 other birth defects were shown to result from chromosomal anomalies, and it was demonstrated that lymphocytes in the blood could be cultured for karyotype analysis — a technical advance that put human chromosomal studies within reach of any scientist or physician who wanted to undertake them. Penrose later remarked of the hereditary mechanism that "the instructional errors, when single genes are involved, are too small to be seen. They are like mistakes made by an imaginary printer whereas chromosome aberrations are like the mistakes of a binder." By the early 60s, human geneticists were equipped with the cytogenetic techniques essential to seeing the binder's mistakes. □

Research in Progress

Making Waves

On March 27, 1964, the Great Alaskan Earthquake, 8.5 on the Richter scale, caused millions of dollars in damage and over a hundred deaths. Ninety-five percent of those deaths resulted not from the earthquake itself, but from a series of devastating waves — tsunamis — that propagated throughout the Pacific Ocean, causing death and destruction as far away as Hawaii, Washington, Oregon, and California.

Crescent City, California, 2,800 kilometers from the earthquake epicenter, was given four hour's notice of the tsunami's arrival. (Although these waves travel through the open ocean at 600-900 kilometers per hour, some warning is occasionally possible.) The first two waves, just two meters high, caused only minor damage. Believing that all was clear, some residents returned to begin cleaning up, only to be met by waves three and four, each about seven meters in height. These waves tossed debris around the town with remarkable force; one of them hurled a gasoline tanker truck against a building, starting a fire that spread to a nearby group of fuel storage tanks, which burned out of control for three days. The tsunami killed 11 people in Crescent City, injured 35, and destroyed 30 city blocks.

No major tsunami has struck the continental United States since that time, so in order to study them Fredric Raichlen, professor of civil engineering, has to make his own. Along with his former students, Joseph Hammack, Derek Goring, and Thierry Lepelletier, and his current students, Costas Synolakis and Jeff Zelt, Raichlen has conducted a series of experiments in two large wave tanks in which he can produce artificial tsunamis. He investigates the characteristics of these waves and the reactions of simulated harbors and shorelines to their impacts.

According to Raichlen, the word "tsunami" comes from the Japanese for "harbor wave." Scientists prefer "tsunami" to the more common, though inaccurate, term "tidal wave" since tsunamis have nothing to do with the tides. Caused by earthquakes, undersea volcanoes, landslides, or other major geological disturbances, most tsunamis are barely noticeable in the open ocean. As swells only a meter above the average sea level, even the largest tsunamis would pass harmlessly under ocean-going vessels.

It's only when a tsunami meets the upwardly sloping ocean floor near an island or continent that its power becomes evident. Raichlen and Synolakis are studying the process of the run-up of these long waves onto beaches. Using the wave tank shown in the photo, they study three types of waves: those that travel unbroken up the beach, those that break before their arrival at the beach, and those that break on the beach itself.

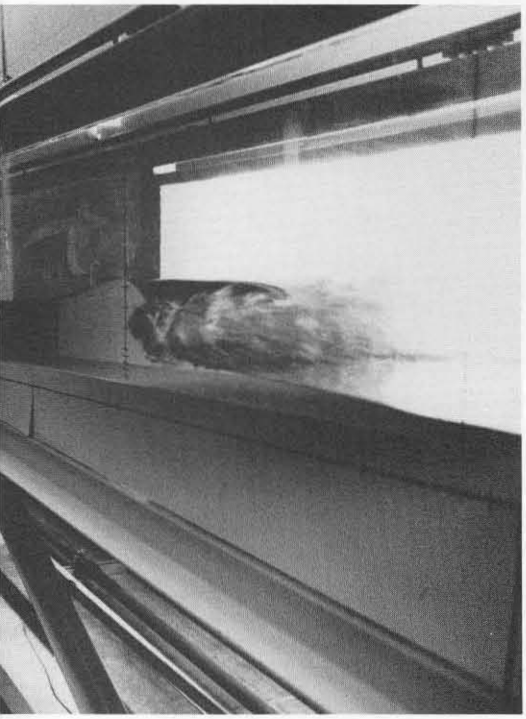
As the Japanese word implies, tsunamis cause great damage within harbors. One would think that harbors with relatively narrow inlets would have a fair chance of avoiding tsunami damage. But it turns out that even certain of these harbors sustain huge amounts of damage from the waves. This happens because the inlet allows the tsunami's energy into the harbor, but then this energy has difficulty escaping. These harbors may actually be "tuned" to resonate at the frequency of the tsunami, causing waves to slosh back and forth in them like coffee in a cup. Much of Raichlen's work is involved with understanding this resonance. Raichlen and student Jeff Zelt perform experimental studies of harbor resonance in a basin 9.6 meters long by 4.7 meters wide in which they bombard simulated harbors with simulated tsunamis. These experiments are useful in developing three-dimensional numerical models of harbor resonance.

Not all of Raichlen's work deals directly with tsunamis. Another of his goals is to determine the internal kinematics of breaking water waves. For these studies, Raichlen and Jim Skjelbreia have equipped the largest of the wave tanks (a tilting one 40 meters

long, 110 centimeters wide, and 61 centimeters deep) with a laser doppler velocimeter. This instrument allows them to determine the speeds of different regions of a breaking wave. To do this, laser light is reflected from naturally occurring tiny particles in the water. The faster these particles move, the more the frequency of the reflected light will shift.

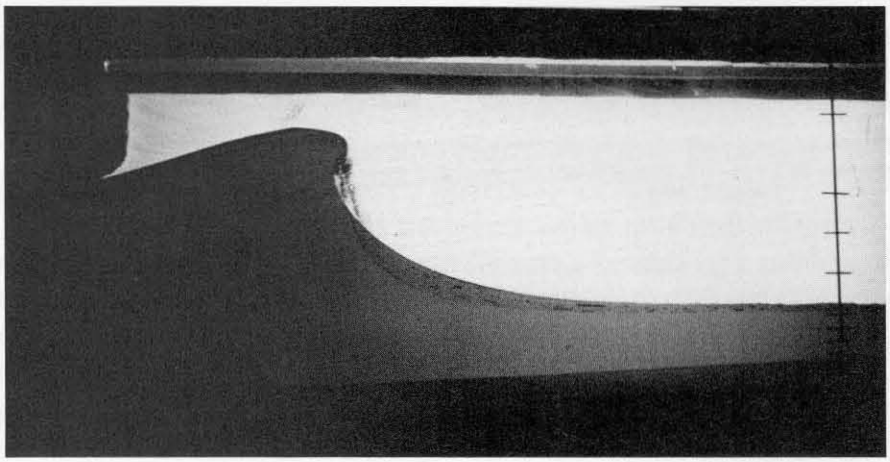
"Such measurements will be helpful in telling us how forces are distributed on a structure when waves impinge upon it," says Raichlen. And the data will also be useful in determining whether a given structure can be designed to withstand tsunamis, or whether the structure will need to be sited farther inland so that it never becomes involved.

Another group of studies, in which graduate student Francis Ting is involved, deals with the interaction of waves with underwater trenches. This



work is important for understanding the aging of navigation channels. Says Raichlen, "If you dredge a navigation channel, and waves propagate over it, you may get into some interesting problems, especially if fine sediments near the bottom turn the fluid into a density-stratified one. Waves can set up internal oscillations within a trench, affecting fluid velocities near the boundaries and modifying erosion processes."

Raichlen receives funding for his work from the National Science Foundation and the Office of Naval Research. □ — *RF*



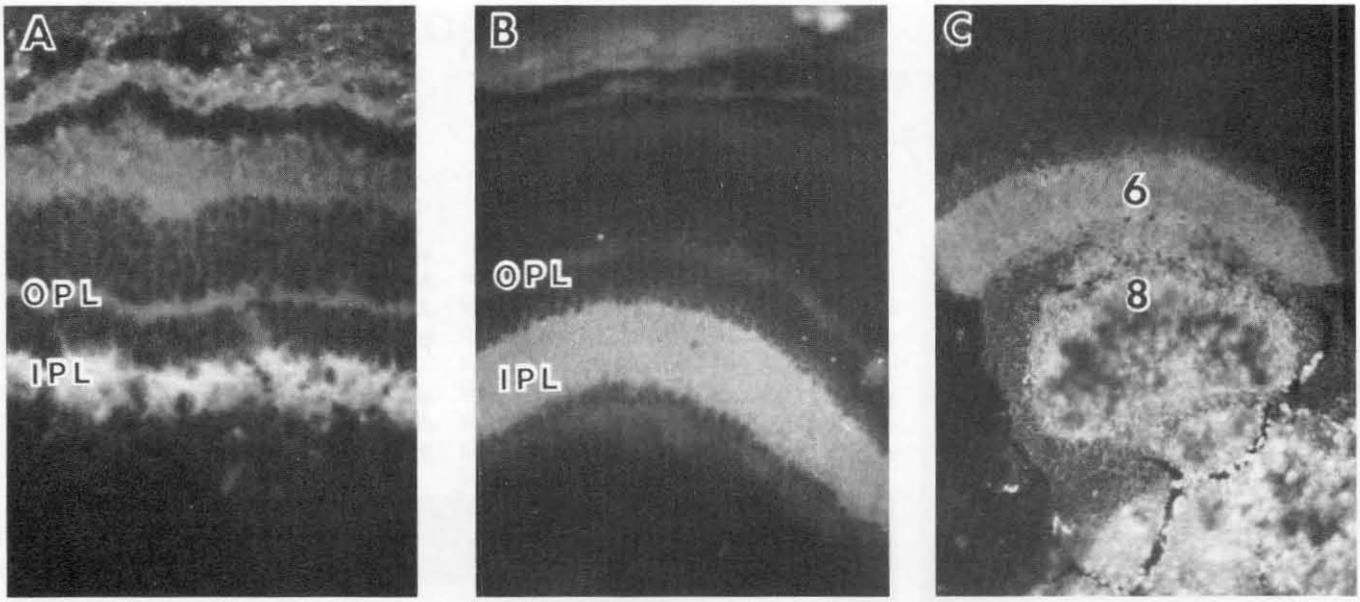
At left Fredric Raichlen and his students watch as a wave crashes in their 37.7-meter-long tank. From left, the students are Francis Ting, Costas Synolakis, and Jeff Zelt. The photo at right has caught a wave just at the point of cresting.

Fly Antibodies and Human Brains: A Marriage of Ideas

CALTECH RESEARCHERS have discovered that our brains have more in common with the brains of fruit-flies than was previously believed. Carol Miller, a visiting associate in biology, has tested a panel of 146 monoclonal antibodies (MAbs) targeted at the *Drosophila* brain on fresh-frozen sections of human brains and found, to her surprise, that over half the MAbs reacted, staining the tissue in interesting and specific ways. This unexpected finding is much more than a mere laboratory curiosity. It may help scientists understand the molecular bases of several devastating neurological disorders, among them Alzheimer's disease and amyotrophic lateral sclerosis (ALS — also called Lou Gehrig's disease).

When she's asked what possessed her to try reacting *Drosophila* antibodies with human brain tissue, Miller answers, with a laugh, "Obviously, a marriage of ideas!" For Miller, who's also Chief of Neuropathology at USC, is married to Seymour Benzer, Caltech's James G. Boswell Professor of Neuroscience. In her study of human brain disease, Miller was about to embark on a lengthy and tedious series of experiments designed eventually to lead to MAbs targeted at the sub-classes of brain cells that these diseases destroy. But Benzer already had in hand his panel of MAbs targeted at the brains of his famous fruit flies. And Miller, noting similarities between some *Drosophila* mutants and some human brain disorders, decided to give his MAbs a try.

No one, to Miller's knowledge, had ever before attempted extensive antibody cross-reactions between such distantly related species. And no one expected such a large proportion of "hits." It's not simply the number of cross-reactions that's surprising. All living things contain many similar molecules, a result of their common evolutionary origins and the constraints imposed by our earthly environment. Some of Benzer's MAbs, for example, bind to the nuclei of all cells, even those belonging to plants like onion and garlic. The really surprising thing in Miller's



One monoclonal antibody stains corresponding regions in (A) the human retina, (B) the mouse retina, and (C) the equivalent of the retina in the fruit fly's eye. IPL and OPL are the inner and outer plexiform layers. Medulla and lamina are 6 and 8.

experiments is the extent of the *specific* cross-reactivity. One *Drosophila* MAb, for example, stains only a certain subclass of cells in the hippocampus, a brain structure involved in memory that receives heavy damage in Alzheimer's disease. Another reacts preferentially with spinal cord motor neurons, which degenerate in ALS.

Like most important scientific discoveries, Miller's prompts more questions than it answers. For one thing, the nature of the molecules — the antigens — to which the antibodies bind is unknown. Are they proteins, glycoproteins, lipids, carbohydrates, or some of each? Are *Drosophila* and human antigens identical or nearly identical, or are only portions of the molecules similar? And what was the evolutionary sequence of events? Is the cross-reactivity the result of convergent evolution in which similar molecules arise from dissimilar ancestor molecules due to common environmental constraints? Or is the cross-reactivity the result of conservative evolution, in which a molecule is simply too important in one certain configuration to permit any evolutionary change, even over hundreds of millions of years?

To answer some of these questions, Miller and postdoc David Hinton are performing immuno-affinity chromatography in an attempt at purifying some of the antigens. In this technique, an antibody is first bound to a solid substrate in a column. Then homogenized brain tissue is poured through the column. The antigen molecules adhere to the immobilized antibodies and remain in the column while everything else passes through. Techniques such as amino acid sequencing can then be used to identify the antigen.

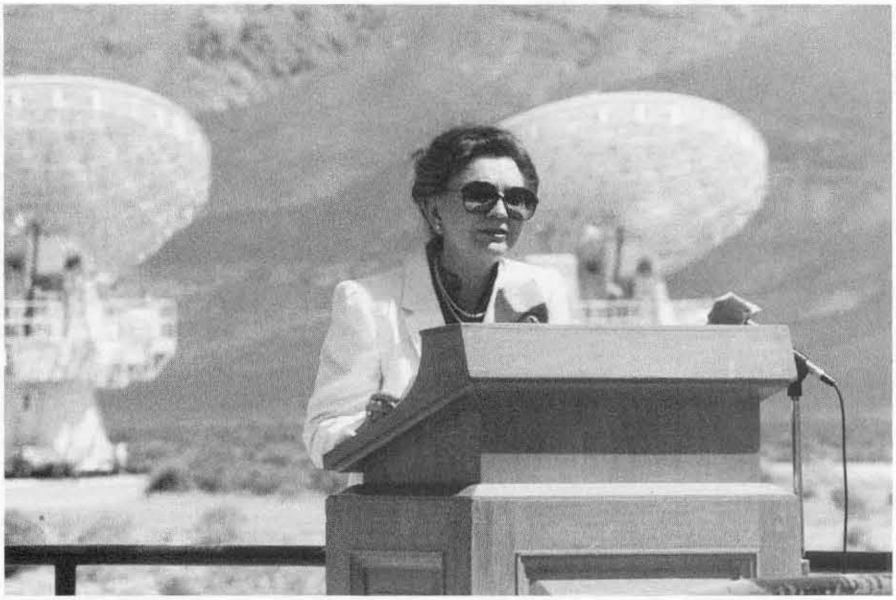
According to some preliminary data, one of these antigens is similar to the protein that makes up the "paired helical filaments," which irreversibly accumulate in, and eventually destroy, neurons in the brains of those afflicted with Alzheimer's disease. This may indicate that a related molecule resides in the normal *Drosophila* brain, encouraging Miller to believe that important aspects of Alzheimer's could be modeled in the fruit fly. This is particularly significant since to date no satisfactory animal model of Alzheimer's disease has been devised.

Miller and Hinton, along with Janet Blanks of the Doheny Eye Institute at USC Medical Center, are also working on a theoretical scheme intended to classify cross-species immunoreactivity in a hierarchical fashion by comparing the eyes of *Drosophila* and *Homo sapiens*. At the apex of the hierarchy would be antigens found only in a single cell in a single species. At its base would be those antigens found in all cells in all species. Intermediate levels of the hierarchy would, for example, group all antigens found in specific neuronal subtypes or all antigens found just in the central nervous system and nowhere else.

Obtaining fresh human brain tissue is one of the more problematic aspects of Miller's work. While animal brains can be obtained immediately after death, it is far more difficult to obtain human tissue quickly after a patient's demise. In addition, brains can't be preserved for these studies by the usual methods, since fixation in formaldehyde or related compounds destroys the reactivity of the antigens with the MAbs. Miller is in a position to ameliorate such difficulties, however, since she's in close touch with the pathology department's autopsy unit. In this way, she can occasionally obtain human brains that have been fresh-frozen less than six hours after death, a remarkably short interval for human tissue. Miller's research takes a lot of effort but it will all be worthwhile if it leads to a deeper understanding of these devastating brain disorders.

Miller's work is funded by the Amyotrophic Lateral Sclerosis Society of America, the Muscular Dystrophy Association, and the National Institutes of Health. Benzer's is funded by the National Science Foundation. □
— *RF*

Opinion



Shirley M. Hufstedler

The Owens Valley Radio Observatory's millimeter interferometer was dedicated before a crowd of 200 guests Saturday, May 4. Consisting of three 10.4-meter antennas acting as a single large radio telescope, the extremely precise instrument will produce high-resolution images at millimeter wavelengths, a new region of the spectrum for astronomical observation. One of the interferometer's principal targets will be the clouds of gas and dust in which stars are born, regions that are opaque to visible and ultraviolet radiation.

Caltech President Marvin Goldberger, Anthony Readhead, OVRO director and professor of radio astronomy, and Laura Bautz, director of the National Science Foundation's Division of Astronomical Sciences, spoke at the ceremony.

The Honorable Shirley Hufstedler, former U. S. Court of Appeals judge and the first Secretary of Education, formally dedicated the interferometer on behalf of the Caltech Board of Trustees by unveiling a commemorative plaque. Before doing so she gave the following address.

I FIND IT unusually fitting that instruments of this quality and elegance should be placed in this setting.

One of the things that I believe is the most impressive about this extraordinary project is the talent and the cooperation that made it possible. Let us realize that this instrumentation can take the ingenuity and reach and imagination of mind and stretch it for billions of years. Let us know that we can see the birth and death of stars while standing here. Let us realize that it is not only the people who have been singled out for special mention today (and they should be), but all of the people that made it possible for those people to work together.

How many generations of teachers of science produced the scientists who produced this great work? How many people whose eyes gazed in the sky so very long ago with the most primitive of instruments caused people to think in the way that made this kind of innovation possible?

Let us remember that the National Science Foundation is supported by taxpayers. It was created by thoughtful people, and it exists because there are enough human beings in this country who know how great science can be when it is left to do the most constructive things.

Let us remember how many craftsmen came here to help. Roads had to be built to this place. People in the town of Bishop had to care. People in this community have to know what these instruments mean and how, in the best of scientific worlds, we now have seen what human talent and cooperation can be. Remember, we have linked institutions. We have linked governments. We have linked the private sector. We have thereby forged a chain of human institutions and responsibilities that permit us to have this great vision into the vastness, the magnificence, and the terror that is the universe.

All the time at OVRO there are people who mind this facility and who care about it, who maintain the gritty things that have to be done — like the roads. But they also maintain these extraordinary instruments. There are people here observing all the time. Here we have six telescopes operated 365 days a year, accurately beyond all imagining to my non-scientific mind. Here we have people who are listening around the clock. We have people who are cooperating with others all over the world who are doing the same thing, thereby expanding the knowledge of all humankind.

Think of how wonderful it would be if we could turn the attention of the world to projects ever more constructive like this. Humankind has the power to create, but it has the power to destroy. Let us be joyful that we can celebrate the power to create on a beautiful day, bringing together all the talent that is here.

It is a very great honor on behalf of the Board of Trustees of Caltech, to dedicate the millimeter interferometer to the service of world knowledge of cosmology. □

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