

A Visitor's View

Max Perutz, Protein Crystallographer

Max Perutz began using x-ray diffraction to look at the structure of hemoglobin in 1937, and he is still looking at hemoglobin — but now he is interested in the abnormal hemoglobin that causes sickle-cell anemia. Perutz, who developed the tools of protein crystallography to solve the structure of hemoglobin in 1953 and won the Nobel Prize in 1962 for that discovery, came to BNL last week as the third Haworth Distinguished Scientist. He spent his days at the Biology Department's Center for Structural Biology and discussed his research in two evening lectures.

Perutz, who created and was the first head of the Laboratory of Molecular Biology at the Medical Research Council in Great Britain, is currently using protein crystallography to design potential drugs against sickle-cell anemia. "Drug firms make 10,000 organic compounds before they produce a marketable drug, and they spend \$60 million to put a new drug on the market," explains Perutz. "We wondered if protein crystallography could be of any help in reducing the cost and time involved in designing new drugs."

As Perutz points out, lowering the cost is especially important for those dubbed "orphan" drugs: drugs combating relatively rare diseases for which no drug company would recoup the cost of conventional development. An anti-sickling drug to treat sickle-cell anemia would be one such orphan.

At a conference on hemoglobin, Perutz was recruited in the search for potential drugs to combat sickle-cell anemia, a chronic, painful and often fatal inherited disorder that mainly affects blacks. It is a recessive disease that causes a reversible transformation of the oxygen-carrying red blood cells. Normally, red blood cells have a biconcave disk shape, but in persons afflicted with sickle-cell anemia, the red blood cells deform and assume the shape of a sickle upon loss of oxygen. The sickled red blood cells are rigid and, as a result, get stuck in the capillaries and cause painful obstructions in the circulation.

Hemoglobin is the iron-containing, oxygen-carrying molecule within the red blood cells, and the hemoglobin of sickle-cell anemia victims differs from



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the normal structure of this protein by a single amino acid. When normal hemoglobin loses its oxygen, it polymerizes into a single filament, but deoxygenated sickle-cell hemoglobin polymerizes into two threads. "It ought to be possible to design some organic compound that opposes the abnormal polymerization," explains Perutz.

During the 1970's, Perutz sought the answer to the question, "How does the combination of oxygen with hemoglobin produce a rearrangement of the subunits of this huge, complex protein?" His x-ray results showed that the natural binding and release of oxygen were accompanied by the movement of hemoglobin's iron relative to the porphyrins, red-pigmented compounds forming the active nucleus of hemoglobin.

Using computer graphics, Perutz explored how the natural chemical which regulates hemoglobin's affinity for oxygen is incorporated into hemoglobin's structure, as well as how

various drugs that affect hemoglobin's oxygen affinity bind. "Our results suggest that the stereochemistry of binding is determined by maximizing the energy of the interaction of charges," explains Perutz. "For example, a drug should be aligned relative to the hemoglobin protein to maximize the mutual polarizabilities of the atoms in contact. This principle had not been realized before in previous drug design work."

The first potential drug examined using the techniques of protein crystallography was dichloromethane, which is conventionally used as an anesthetic, the structure and anti-sickling activity of which were discovered by Benno Schoenborn, head of BNL's Center for Structural Biology. Because it does not bind strongly with the hemoglobin, dichloromethane was ruled out as a potential drug since the concentration needed to produce an anti-sickling effect would be considerably above the tolerated dose.

Perutz and his collaborator Donald

Abraham of the University of Pittsburgh then considered the diuretic ethacrynic acid because it had similar properties and fit the same binding site as dichloromethane. Because it is more reactive with hemoglobin, they thought it could be administered in a lower concentration. "From the clinical point of view, however, you can't treat sickle-cell patients with a diuretic because they are already severely emaciated," explains Perutz.

They next considered a derivative of ethacrynic acid that lacked the diuretic property, but that bound to the same site. However, it had a flaw: It bound strongly with the albumin in blood serum. "We might get a usable compound if we replace one of the radical groups with another that would weaken or abolish the binding to serum albumin," adds Perutz.

Another compound Perutz considered, bezafibrate, lowered the oxygen affinity of hemoglobin more than the natural chemical regulator did. "Clinicians says this drug would be useful to treat heart attacks because it would improve the delivery of oxygen to deprived tissue. But again, the concentration required to produce a physiological affect on hemoglobin was too high." Perutz's collaborators are attempting to alter this compound so that the dose can be lowered.

Perutz found that succinyl tryptophan tryptophan has the same affect as bezafibrate, but binds to a different site on hemoglobin. Says Perutz, "What this tells us is that drugs may change the response of a protein in the same way a natural hormone does, even if the synthetic compounds are chemically unrelated to the natural stimulus and bind to quite different sites. Proteins may offer a variety of binding sites that are not used in nature, but which can be taken advantage of in drug design."

Despite the difficulties he has encountered, Perutz is continuing his x-ray analysis and structural determination of potential anti-sickling compounds in collaboration with French and American researchers. He spent 25 years solving the structure of hemoglobin, and now he is binding his basic interest in protein crystallography to a practical need for a medical cure. — Marsha Belford

BNL Lecture: The Tie That Binds

Neutrinos and electrons are some of the constituents of matter. They have no discernible structure, at least for now, which means they are as simple an entity as we know. The force between them has been understood in detail in the last few years, as the electroweak theory of Glashow, Weinberg and Salam has gained acceptance. Physicists believe that the force is mediated by vector bosons, which were first predicted by the theory and then observed at CERN in collider experiments.

In the next Brookhaven Lecture, Senior Physicist Hywel White will discuss the work at BNL in a talk entitled "Neutrinos, Electrons and the Tie That Binds." The lecture will begin at 4:30 p.m. on Wednesday, April 9, in Berkner Hall.

"Here at Brookhaven," says White, "since we cannot make vector bosons directly, we have been going at this problem in another way. When two particles are scattered, the force that causes the scattering may be studied by careful measurement of the rate at

which scattering takes place. At the AGS, beams of neutrinos are made and collided within massive detectors, massive because the force is so weak.

"In neutrino beams at the AGS at first, the 7-foot bubble chamber produced exciting physics in hydrogen with the observation of charm. Later, the ambition to scatter neutrinos from electrons meant that much more massive detectors were required."

In his lecture, White will talk about the collaboration of Brookhaven, Univ. of Pennsylvania, Brown, KEK, Osaka and SUNY at Stony Brook, which built and ran a 200-ton electronic detector at the AGS, specifically designed to observe neutrino electron scattering. According to White, the connection between the mass of the vector bosons and the rate of scattering has held up and, at least for now, the theory is secure.

Hywel White was born in Wales and educated there. After receiving the B.Sc. from the University of Wales, he left for England and the University of Birmingham where he obtained his

Ph.D. in 1956. After two years at Birmingham as a research fellow he came to the United States and taught for the next four years at the University of Pennsylvania. In 1964, White joined the faculty of Cornell University and remained there as professor of physics until 1978.

In July of that year, White came to Brookhaven as a senior physicist in the Accelerator Department. He headed the Experimental Facilities Division of Brookhaven's colliding beam accelerator project. From 1981-1983 he was deputy chairman of the Accelerator Department and, since 1983, has devoted himself to physics research, particularly neutrino scattering. Currently he is a member of the scientific staff of the Physics Department and is spokesman for neutrino Experiment 734, which is taking data in the neutrino beam at the AGS.

All those interested in getting together after the lecture are invited to go with the lecturer to a restaurant off

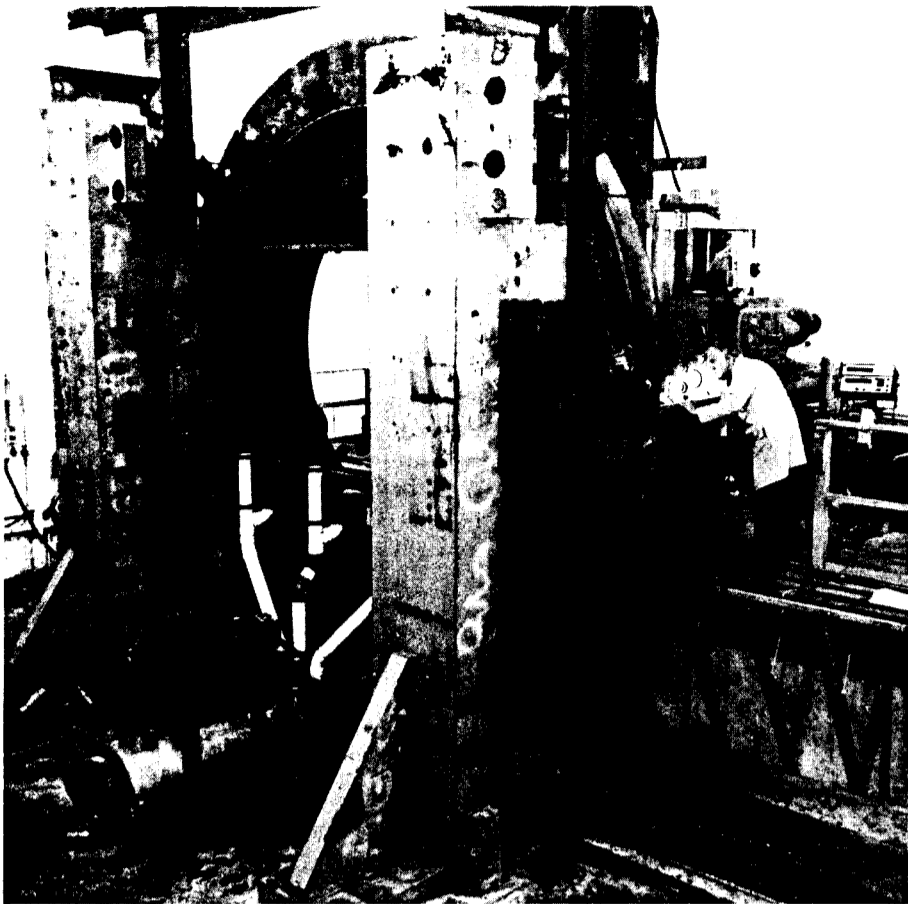


Hywel White

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site. If you want to be part of this group, Call George Rabinowitz, Ext. 7637.

Not To Be Taken Lightly



Mort Rosen

In the Wide Angle Hall, Larry Fanella, Central Shops, uses a traveling column machine to bore 5-inch diameter holes through a 16-foot diameter, 24-inch thick steel ring that will be part of a detector for Experiment 787 at the Alternating Gradient Synchrotron.

Employee Suggestion Leads to New Data Base and Travel Form

Richard W. Leigh and James H. Saunders Jr., both of DAS, concluded that it was quite possible to spend several hundred dollars for the proceedings of a conference, which seemed a waste of money as probably a Lab staff member who had attended the conference had a copy of the proceedings. But there was no way to find the person or persons who had attended the meeting. So Leigh and Saunders sent in a suggestion to the Employee Suggestion System.

They proposed the establishment of a central data base, which would contain information about conferences attended by Lab employees and whether or not the employees had a copy of the proceedings in their possession. Leigh and Saunders also suggested that obtaining this information should be a routine part of making travel arrangements for conference-bound employees. The data base would be maintained by the Research Library and would be accessible to all interested employees.

The Research Library accepted the suggestion and has established a Conference Attendance and Proceedings System (CAPS). This microcomputer-based file will store and keep track of a number of data elements, most of which are gleaned from a revised Standard Travel Authorization (STA) form completed by the employee, and copy sent to the Research Library. The new STA is form BNL F63D, and previous versions should be discarded.

The Research Library staff will follow up on the information on the new forms, noting in the data base the availability of the conference proceedings and whether attendees will loan or share copies. The Library will, of course, continue to purchase or accept donations of conference proceedings for cataloguing and placing in various library collections throughout BNL. The system will supplement existing on-line data bases and catalogs and will be continually updated.

Deisenhofer Reports on Photosynthesis

Crystallographer Johann Deisenhofer, from the Max Planck Institute for Biochemistry, will give a seminar on Monday, April 7, at 11 a.m. in the Hamilton Seminar Room, Bldg. 555. He will summarize the work that he and colleagues have done in crystallizing a reaction center of a photosynthetic bacterium. His talk is entitled "X-ray Structure of the Photosynthetic Reaction Center of Rhodospseudomonas Viridis."

Deisenhofer's findings are the result of work that has been pursued for years by scientists trying to better understand photosynthesis. In both photosynthetic bacteria and green plants, the reaction center is the magic box where light is converted into chemical energy. Isolation of reaction centers was done in the 1960's, and about ten years ago, laser techniques in the picosecond time frame were developed to study rates of reaction.

Knowing the x-ray structure of the reaction center means knowing in detail what the molecules are, how they are arranged and what their

environment is. From that information, scientists may be able to build molecules in similar arrangements — essentially, to synthesize photosynthesis.

This important work has greatly advanced the understanding of photosynthesis. It also has broad applications in electron transfer theory and in protein crystallography and chemistry.

Diners Note

The Cafeteria will be closed on Saturday, April 12. On that day, snack bar service will be available from 9 a.m. to 2 p.m. at the Brookhaven Center.

All film badges will be changed tomorrow. Please place your badge in its assigned rack space before leaving work today.

When you're working with 420 tons of steel, you certainly don't take the job lightly. Since last summer, the Central Shops Division has been making steady progress building a detector that, in sheer weight and size, is one of the biggest projects tackled by the division. It's required some creative solutions to unusual problems, says Division Manager Richard Spellman, plus many hours of plain hard work.

The detector is for Experiment 787 at the Alternating Gradient Synchrotron (AGS). As described by one physicist, picture a horizontal steel cylinder two stories high, filled with a couple of miles of copper conductors and hundreds of scintillation counters, the whole thing designed for a study of subatomic particles called K mesons. Central Shops is doing the steel work.

The steel comes from a 2,700-ton synchrotron that BNL got as surplus several years ago from the Space Radiation Effects Lab in Newport News, Virginia. The part used in the AGS detector consists of eight disks, each about 16 feet in diameter, one foot thick and weighing about 52 tons.

Jobs of this size are normally done in the heavy machine shop, says Spellman, but the building and its crane capacity were too small. Fortunately, they got approval to use the Wide Angle Hall in the CBA ring, and that's where most of the work is being done.

Basically, the major tasks have included burning out the centers of disks to form rings, cutting arcs out of the centers and welding them together to make additional rings, cutting foot-wide slots to let copper conductors through, welding rings together to make pairs, boring 5-inch diameter holes through them for alignment and coil supports, and welding on stands. Still to be bored are about 400 3-inch diameter holes.

All the boring is in the hands of Tool and Instrument Makers Larry Fanella and Gerald Greenidge, who use a special machine on loan to the Lab. When you walk into the Wide Angle Hall, you are struck with the enormity of the operation. Besides being huge, the machine sits on a platform five feet off the floor, the elevation necessary because of the size of the rings.

Group Leader Fanella explains what it takes to bore a 5-inch hole through a welded pair of rings. The first pass is made with a 4 3/4-inch cobalt bit and takes four hours non-stop. Then a 5-inch carbide bit is used to prebore a hole about 6 inches deep,

which takes 15 minutes. Finally, another 5-inch carbide bit is used to go the remaining 18 inches, adding 1 1/2 hours to the job.

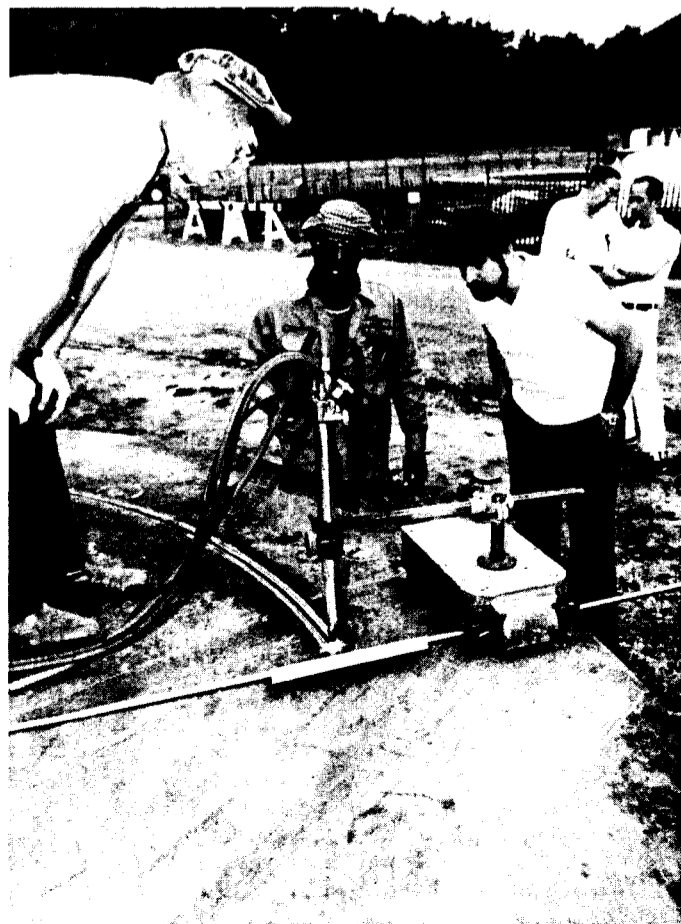
If the boring seems time-consuming, however, don't think the welding and cutting jobs are any different. Carl Gardner, who cut the centers out of eight disks, says it took 2 1/2 hours to do each one. And welding two rings together took 40 hours, according to Robert Geib, who shares welding duties with Mark Cohen, Walter Ducioing, Group Leader John McCaffrey and Richard Savoy. Henry Floege has been providing assistance on all jobs.

The one thing about welds, says Geib, is that they simply must not fail. For example, one job the welders have to do is attach eyes (the size of a hand) to the rings so they can be maneuvered by crane. It may take 6 hours to properly weld on one eye, but when you see a 55-ton disk lifted by that one piece, you don't begrudge the time.

Central Shops started on the detector last summer and work has progressed steadily. It's been an unusual job not only because of the size and weight of the material, but also because of logistics problems, says Spellman, referring to the difficulty of moving such massive material and to the constant ferrying of men and tools back and forth from the shops out to the Wide Angle Hall. He credits the riggers in Plant Engineering who have been called on repeatedly to move the steel around.

The detector represents one extreme of the kinds of jobs done by Central Shops. Says Deputy Manager Enrique Jimenez, "We also work on the miniature scale where we have to drill holes less than the diameter of a human hair. So we go the full gamut." Last year, the division's 25 staff members, including supervisors, and 84 shop personnel handled about \$6 million of fabrication work. Of that, about \$4.75 million was done in-house and the balance was subcontracted out. But no matter where the jobs are done, all the associated paperwork and inspections are handled by the division.

Adds Spellman, "In the past, big jobs like this detector traditionally came from the AGS and Physics Departments. Now, we also have the Light Source and High Energy Facilities requesting large fabrication, with ten other departments requesting smaller jobs." He credits the entire division for pulling together as a team. "Without that, we couldn't possibly produce the amount of fabrication work that we do." — Mona S. Rowe



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From left, John McCaffrey and Carl Gardner, Central Shops; and Richard Rosenska, Physics, monitor the progress of a flame cutter that Gardner is guiding around a disk to cut out its center. In the background are Irving Polk, a consulting engineer, and Kelvin Li, Physics, who is on the experiment and managing the detector construction.

BERA News

Concert Notice

The concert at Berkner Hall on Tuesday, April 15 will not be given by the Musica Da Camera Praga, as previously announced, but instead by the Cremona Arts Trio. The Trio's performance on the night of the 15th will begin at 8:30 p.m. Tickets will be available at the door. General admission is \$9; students and those over 65, \$6; and those under 18, \$5.

Afro-American Club

The members of the Afro-American Culture Club would like to congratulate Bruce Penn and Rose Lawrence for their success in the election for club president and treasurer, respectively. We would also like to thank Robert Mosley and Abass Wesson for running. It was the closest election the club has had.

Cooking Exchange

The Cooking Exchange meeting on Wednesday, April 9, will feature traditional Japanese and Chinese cookery.

Meetings are held in the Recreation Building between 12:30 and 2:30 p.m. and are open to employees and their immediate family members. A small donation of \$1.25 per person entitles those present to a copy of the day's recipes, samples of the dishes prepared and coffee or tea. Babysitting is provided at 50¢ for each child.

For more information, call Madoka Miake, Ext. 3131; Sara Morse, Ext. 1712; or Susan Sears, 744-7831.

Singles Club

The monthly meeting of the Singles Club will be held on Tuesday, April 8, in the Berkner Hall lobby from 12:20 p.m. to 12:40 p.m. Ideas for summer activities are needed.

Rifle & Pistol Club

The regular monthly meeting of the BNL Rifle and Pistol Club will be held on Wednesday, April 9, at 5:15 p.m. in Room 202, Building 911B. All interested are welcome to attend.

Volleyball

League I	W-L
Dinkers	49-4
UpFagrabs	38-15
X-Rayted	28-25
Bumpers	24-29
Net Results	11-42
TNT	9-44
League II	W-L
Phoubars	53-0
Nuts & Bolts	31-22
Fossils	25-28
Chungas Revenge	24-29
Cannonballs	22-31
Upton-Ups	4-49
League III	W-L
Print-Outs	39-18
Foul-Ups II	37-20
Screwballs	31-26
The Buddys	27-30
Light 'n Lively	20-37
Couples	17-40
Open League	W-L
Odds & Sods	41-7
Dakota	40-8
Phoenix	33-15
Court Jesters	22-26
Rowdy Radicals	20-31
Generic	13-38
Out of Control	2-46

Basketball

Game 1	Score	Game 2	Score
Longshots	69	Runaways	68
L. James	8	G. Shepherd	2
P. Brown	3	T. James	15
J. Garrison	6	P. Johnson	16
R. Seymour	18	G. Smith	2
L. Walcott	26	R. Moran	11
E. Taylor	2	J. Desmond	20
B. Johnson	6	A. Stillman	2
Hollywood	86	Coasters	45
G. Mack	10	M. Williams	8
R. Domenech	22	P. Ratzke	26
R. Kowalski	8	L. Lawrence	7
E. Meier Jr.	20	R. LeRoy	4
B. Gunther	6		
J. Powell	4		
D. Hall	2		
D. Nordstrom	14		

Astronomical Society

The Astronomical Society is now recruiting new members. Those unfamiliar with our domed observatory and eight-inch reflecting telescope should attend the next open observation night on Friday, April 4, at dusk or, in case of rain, one week later. The society plans to upgrade to a 14- to 16-inch instrument within the coming year. Annual dues for the society are \$15 per calendar year. Contact Bob Mills, Bldg. 901, Ext. 5043, for details.

The Brookhaven Bulletin of March 28 contained a report of responses to the question "Have you seen Halley's Comet?" For those who have not or for those who want one last look, the Astronomical Society will host a "Farewell to Comet Halley" celebration on Friday, May 2. The event will feature a 45-minute talk on Halley's Comet and comets in general, delivered by the Director of the Vanderbilt Planetarium, at 7:30 p.m. in the North Room of the Brookhaven Center. The talk will be followed by refreshments and a trip to the observatory for a viewing of the comet, which will be in a good position for the society's instrumentation in the early evening, weather permitting.

Admission is \$7.50 for adults, \$3 for children under 14 and substantially less for Astronomical Society members. Contact Mark Levine at the Vanderbilt Planetarium, 757-7501, for details and reservations. In case of poor atmospheric conditions, the viewing will be postponed to the next appropriate evening. For further information, also call Mills, Richard Jackimowicz, Ext. 3803, or Karin Karlstrom, Ext. 4398.

Bowling

White League

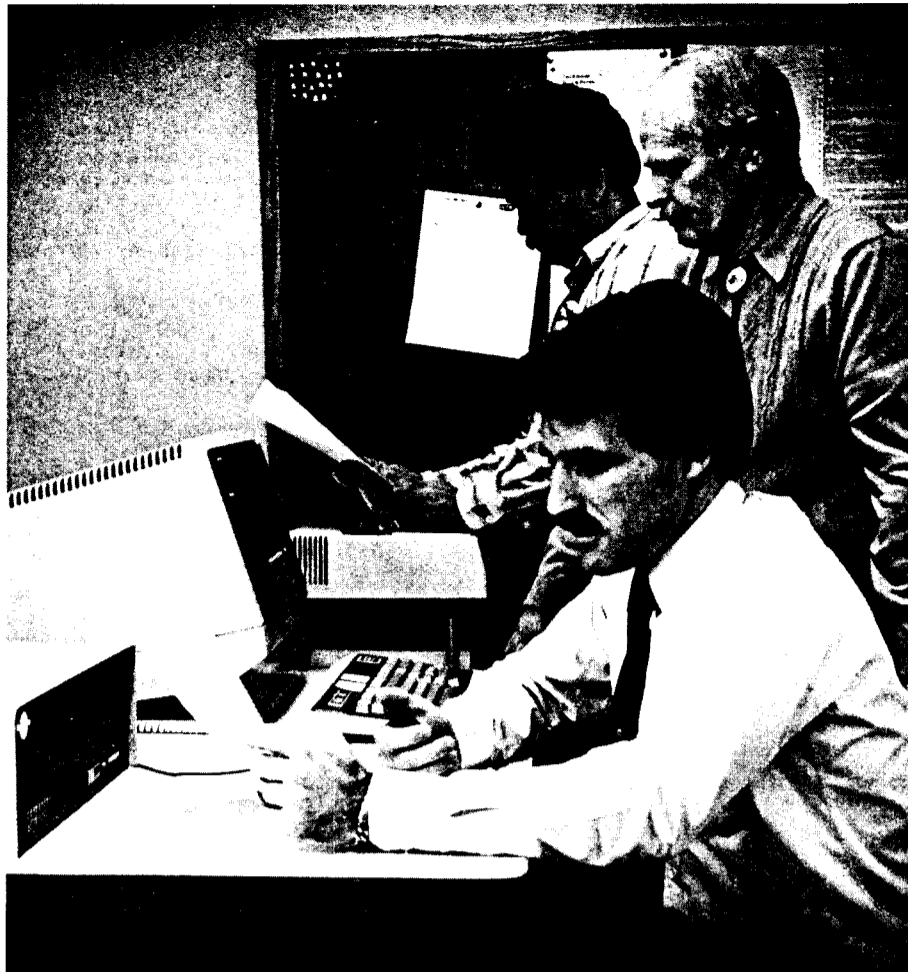
High games were bowled by Jim Roesler 233, Ben Belligan 211, Vito Manzella 211, Tom Sperry 211, Ken Riker 209, Terry Skelaney 199, Lorraine Petro 196, Pat Manzella 193, Joyce Mortimer 187, Maryanne Rignola 185.

Red/Green League

J. Elmore rolled a 223, P. Ouvrard 222, J. Ferrante 209, E. Meier 208, H. Marshall 206, W. Kristiansen 201, L. Jacobson 201.

Purple League

Gene Hassell had a 226, Ed Meier 225, Sharon Smith 212, Ken Asselta 212, Ken Riker 207, Joe Ferrante 201, Betty Jellett 193.



Peter Horton

The Weather Watchers

When you dial the weather forecast number, Ext. 2263, you now get the weather report on a recording made by one of the Lab's meteorologists. In the new system, a weather forecast is recorded on an answering machine at around 9 a.m. and updated at 3 p.m. Shown setting up for a recording are, from front to back, Leonard Dupuis, Robert Brown and Martin Leach. According to Brown, the weather forecast

number is called an average of 35 times a day. "Before, we were spending a lot of time answering the phone," says Brown. He adds that even other people in Bldg. 51, where the meteorology equipment is located, were having to deal with callers by trotting off to find the printed forecast prepared each day by a meteorologist. Now there's an answering machine that doesn't care who calls when.

Join the BNL Team

Each year the Long Island Chapter of the March of Dimes conducts a walkathon to raise money for the Birth Defects Foundation in support of research, medical services and educational programs. For the past two years a team of BNL employees joined walkers from over 225 corporations and organizations to help make this annual event successful.

Walk America, as the event is called, will be held on Sunday, April 27, starting from Smith Haven Plaza in Suffolk County, and Eisenhower Park in Nassau County. Laboratory employees who would like to join this year's team may pick up information sheets and registration forms from the Recreation Office in Personnel as soon as possible; definitely before April 16.

Arrivals & Departures

Arrivals

Scott W. Buda NSLS
David R. Harding Chemistry
Jannifer E. Hill Medical
Jan Kieleczawa Biology
Hans J. Willutski Physics
Min-Hsiung Yang Plant Eng.

Departures

This list includes all employees who have terminated from the Laboratory, including retirees:

Harpal S. Arora DNE
Jeffrey A. Campbell Chemistry
Sylva M. Cohn Mgt. Info. Sys.
John M. Densieski Chemistry
Sheikh M. Hadi Biology
Nelson A. Hanan DNE

Classified Advertisements

Placement Notices

The Laboratory's placement policy is to select the best-qualified candidate for an available position, with consideration given to candidates in the following order of priority: (1) present employees within the department and/or appropriate bargaining unit, with preference to those within the immediate work group; (2) present employees within the Laboratory as a whole; and (3) outside applicants. In keeping with the Affirmative Action plan, selection decisions are made without regard to age, race, color, religion, national origin, sex, handicap or veteran status.

Each week, the Personnel Office lists new personnel placement requisitions. The purpose of these listings is, first, to provide open placement information on all non-scientific staff positions; second, to give employees an opportunity to request consideration for themselves through Personnel; and, finally, for general recruiting purposes. Because of the priority preference policy stated above, each listing does not necessarily represent an opportunity for all candidates. As a guide to readers, the listings are grouped according to the anticipated area of recruitment.

Except when operational needs require otherwise, positions will remain open for one week following publication date.

For further information regarding a placement listing, contact the Employment Manager, Ext. 2882.

THE VACANCIES LISTED BELOW HAVE BEEN EXEMPTED BY THE DIRECTOR'S OFFICE FROM THE CURRENT FREEZE ON OPEN REQUISITIONS.

OPEN RECRUITMENT - Opportunities for Laboratory employees and outside applicants.

2416. PLUMBER - (2 positions) - 5/19/86 - 10/10/86. Requires successful completion of four-year apprenticeship program and/or substantial experience in the commercial/industrial sector. Will be responsible for the layout, construction, installation, repair and maintenance of water, sewage and gas systems, related facilities and auxiliary equipment. Plant Engineering Division.

2417. STEAMFITTER - 5/19/86 - 10/10/86. Requires substantial experience in the commercial/industrial sector. Will be responsible for the layout, construction, installation, maintenance and repair of heat, steam and water distribution systems, related facilities and auxiliary equipment. Plant Engineering Division.

2418. P&GA SPECIALIST - Requires a minimum of two years' experience in the operation of the AM Vartyper Comp/Edit 5810 phototypesetter and its associated equipment. Familiarity with scientific and tabular typesetting required. Must possess good "paste-up," proofreading and English skills. Photography and Graphic Arts Division.

(Continued on page 4)

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