Lynch wants to know if the messenger RNA for the von Willebrand factor made in endothelial cells is even the same as the message made in megakaryocytes. "In megakaryocytes, von Willebrand factor is stored as multimers in the cells. In endothelial cells, the bulk of the protein is in the form of dimers. Why is that? Is it exactly the same protein or is it a slightly different form?" he asks.

A final consequence of having the cloned von Willebrand gene is that investigators should be able to sort out at last the confusing variations of von Willebrand's disease. "Von Willebrand's disease is the thalassemia of coagulation," says Ginsburg. In thalassemia, there were multiple subtypes and variants, all clinically defined and hard to understand until molecular biologists, including Orkin, analyzed the genes involved and were able to explain the thalassemia variants on a molecular level.

"Hemophilia is fairly straightforward," says Ginsburg. "In general, the less factor VIIIC activity you have, the more severe the disease. But with von Willebrand's disease, there are all different kinds of subtypes. Type I is most common, but now there are types Ia, Ib, and Ic. There also are types IIa, IIb, and IIc as well as a type III." People with type II von Willebrand's disease, for example, make normal amounts of the protein but the protein itself is abnormal. Some type II's make proteins that do not aggregate properly and others make proteins that are overly active and bind too tightly to platelets. "It's a real morass," Ginsburg remarks.

But with the cloned gene in hand, molecular biologists should be able to pinpoint the causes of the different subtypes of von Willebrand's disease, making the classification of the subtypes more rational and diagnosis easier. In addition, the subtypes undoubtedly include mutant proteins that are not processed properly, and by studying them, investigators should learn how the von Willebrand factor is processed. Already, they know it starts out as a 300,000 dalton precursor and ends up as 220,000 dalton subunits which then aggregate to form complexes with molecular weights as high as 20 million. By studying the various mutant proteins, they should be able to learn what happens to this protein along the way to its final destination in the blood.—GINA KOLATA

Los Alamos Neutron Source Meets First Test

Storing a beam in the proton storage ring means a world-class source is in sight, but money for an experimental hall is lacking

26 April was a day for celebrating at the Los Alamos National Laboratory as jubilant researchers stored a beam in the Proton Storage Ring (PSR) on the very first attempt. The PSR is a $22-million addition to the Weapons Neutron Research (WNR) facility whose effect will be to convert the WNR into a world-class pulsed source for neutron scattering on a par with the British Spallation Neutron Source that recently entered the commissioning phase at the Rutherford Appleton Laboratory (*1*). The combined WNR/PSR facility will be dedicated this August as the Los Alamos Neutron Scattering Center (LANSCE).

However, two important provisos to be satisfied before researchers can tap the intense neutron beam the WNR/PSR will provide are the construction of an experimental hall sufficiently large to house research instrumentation and the development of the instrumentation itself. Now set at $17.5 million, funding for this purpose has never made it into the presidential budget. "Without a substantial increase in money, Los Alamos will have a first-rate source of neutrons that can't be effectively used," sums up J. Michael Rowe of the National Bureau of Standards (NBS), which itself has been trying to obtain support for a research facility for very long wavelength (cold) neutrons around its own reactor-based neutron source.

This year the House Committee on Science and Technology, in its markup of the Department of Energy (DOE) civilian research and development authorization bill, directed DOE to begin funding construction of the experimental hall in fiscal 1986. The committee authorized $1 million for this purpose (to be accommodated by a decrease elsewhere in DOE's budget), with a total of $18.4 million to be reached during the following 2 years. Whether these directives survive in the full House or in the Senate and whether funds are ultimately provided in the all-important companion appropriations bills are, of course, uncertain given the widespread concern over the national budget deficit.

The WNR/PSR is important to U.S. neutron scatterers because it addresses the two most important issues facing the field: providing facilities equal to those of researchers elsewhere in the world and laying the groundwork for the higher intensity neutron source that will be needed in the 1990's to replace the reactors that are the mainstays of the present program.

Driving much of the concern is the specter of European and, increasingly, Japanese competition. Observers generally agree that, starting in the 1970's, European researchers have gradually wrested away leadership in neutron scattering from their American colleagues. The British-French-German Institut Laue-Langevin (ILL) in Grenoble, whose reactor started up in 1971 and whose budget alone matches that of the entire U.S. neutron scattering program, symbolizes that leadership.

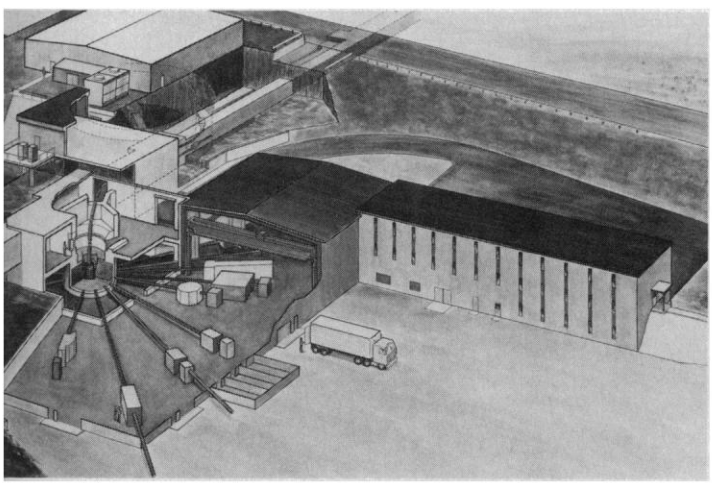
With a flux of 1.5×10^{15} thermal neutrons per square centimeter per second (neutrons/cm^2-sec), the ILL reactor is no more intense than comparable reactors at Brookhaven National Laboratory and Oak Ridge National Laboratory. But a combination of a more versatile reactor design, large numbers of experienced scientists, and adequate resources has allowed the maximum exploitation of the available neutrons. Special moderators (cold sources) generate very low energy neutrons that give details of large complex molecules (polymers and biological macromolecules) not obtainable with ordinary thermal neutrons. Guide tubes coated with neutron-reflecting material transport the neutrons large distances, allowing more instruments around the reactor and in some cases greatly enhancing resolution. And instruments of improved resolution and sensitivity effectively multiply the neutron flux.

Moreover, the ILL is hardly the whole show. According to a recent compilation by Roger Pynn and Brian Fender of the ILL, while that facility has 26 neutron scattering instruments surrounding its reactor at present (seven more will be ready this fall), overall in Western European nations there are 110 neutron scattering instruments at the 11 reactors providing a flux of 10^{14} thermal neutrons/ cm^2-sec or more (*2*). The comparable American figure is 42 instruments at 5 reactors in this flux range, according to a study by Ralph Moon of Oak Ridge (*3*).

Despite the imbalance in facilities and resources, American neutron scatterers have managed to maintain leadership in some important research areas. A 1984 National Research Council panel headed by John Rush of NBS identified two of these as thermal neutron triple-axis spectroscopy and chemical and biological crystallography (*4*). The panel also placed the United States in the forefront of pulsed neutron research, but this was before Rutherford's new source was completed.

three times the ILL neutron flux. Although this increase is in line with past improvements in neutron flux, a still larger increase requires new ideas for the reactor core, where handling the intense heat load is the limiting factor.

Pulsed sources generate neutrons when the accelerated proton beam strikes a target made of uranium or another heavy metal. Each proton chips away 20 or so neutrons from the heavy metal nucleus it strikes, hence the name spallation source. Assuming accelerator technology for high-current proton accelerators of the type needed to generate intense neutron pulses progresses, the potential for significant increases in neutron flux from pulsed sources over reactors exists because the heat generated in the target can be removed between the pulses.



LANSCE

The proposed experimental hall (foreground) and laboratory and office building (right) abut the existing WNR facility. The PSR is the circular structure under the building at the top-left.

Pulsed sources, which use proton accelerators rather than reactors to generate neutrons, are of interest on two grounds. The first is that they are complementary to the steady-state reactor sources. In particular, the spectrum of neutrons spewing forth from pulsed sources extends to kinetic energies of 1 electron volt and higher (so-called epithermal neutrons), whereas the spectrum from reactors peaks at the thermal energy of about 0.025 electron volt. The current conventional wisdom is that reactors are superior for low energy or slow neutrons, whereas pulsed sources are superior at higher energies.

The second reason to consider pulsed sources is to increase the available neutron flux. Although U.S. research reactors are mostly 20 years old or more, reactor technology is on a plateau, so that there is no immediate prospect of building a new reactor with a greatly increased neutron output. Oak Ridge, for example, has been working on a conventional design that would generate about

The main problem with the pulsed neutron source option is that the necessary experience in operating pulsed machines and doing experiments with them is not yet in hand. An advanced pulsed source would likely cost over \$300 million to build and \$25 million per year to run, while each research instrument, such as a spectrometer or diffractometer, would carry a price tag of over \$1 million. Future approval of such a facility plainly requires the accumulation of such experience.

Partly for this reason, a National Research Council panel charged with establishing priorities for so-called major materials research facilities, in a report issued last July, rated an advanced reactor over a pulsed source for a next-generation neutron facility (*5*). However, the panel, which was co-chaired by Frederick Seitz of Rockefeller University and Dean Eastman of the IBM Yorktown Heights Laboratory, recognized that the WNR/PSR is the next step for U.S. neutron scatterers in acquiring experience with pulsed sources and recommended the funding of the proposed experimental hall.

Since then, two other reports have supported the findings of the Seitz-Eastman panel. Last month, DOE's Energy Research Advisory Board called for the incorporation of advanced target and cold source concepts, such as those recently developed at Argonne National Laboratory, at both the Argonne and Los Alamos facilities before plunging ahead with an advanced pulsed source (*6*). The board also urged "an immediate commitment to construction of the experimental hall and key instrumentation" at Los Alamos.

The consensus of those attending a neutron scattering workshop that was held at Shelter Island, New York, last October with the aim of making a case for the advanced neutron source of the 1990's was slightly fuzzier (*7*). While reiterating their support of the Seitz-Eastman panel priorities, the researchers concluded that the most important thing is to achieve higher neutron fluxes than are now available from either type of source. About 80 percent of presently conceivable experiments could be done equally well with either steady-state or pulsed sources, whereas the other 20 percent would do better with one type than the other, the researchers agreed.

The important characteristics of pulsed sources are the neutron flux during the pulse (peak flux), the length of the pulse, and the pulse repetition rate. For most experiments, a high peak flux, short pulse length, and low repetition rate represents the optimum combination. The peak flux from a pulsed source cannot be directly compared with the flux from a reactor, but the Shelter Island conferees agreed that an advanced reactor of average flux 5×10^{15} neutrons/cm^2-sec and pulsed source of peak flux 10^{17} neutrons/cm^2-sec and repetition rate near 50 pulses per second would have similar capabilities.

At present the most intense pulsed neutron source in the United States is the IPNS at Argonne, which has pioneered the development of this type of source. Money to build the IPNS, which opened in 1981, was the only bump on an otherwise flat neutron scattering funding profile since the spate of reactor building in the mid-1960's. However, while the IPNS has a peak flux of 4×10^{14} thermal neutrons/cm^2-sec in pulses coming 30 times per second, the WNR/PSR at full power will jump to 10^{16} neutrons/cm^2-sec pulses at a rate of 12 per second. As for the future, both Argonne and the Jülich Nuclear Research Center in West

Germany have plans, though based on two different types of accelerator technology, for the next generation pulsed source of flux 10^{17} neutrons/cm^2-sec.

Given Argonne's depth of pulsed neutron source experience, why is the WNR/PSR at Los Alamos? The primary reason is the prior existence of the powerful Los Alamos Meson Physics Facility (LAMPF) accelerator. This machine is an 800-meter-long proton linear accelerator that was dedicated in 1972 for nuclear physics research. Over the years its performance has improved and it now generates both proton and negative hydrogen ion beams having a time-average current of 1 milliampere and energy 800 million electron volts. The current is the key characteristic. For comparison the proton synchrotron at Argonne accelerates 12 microamperes.

In 1977, the WNR was appended to LAMPF to generate neutrons for defense-related nuclear physics and materials science research. For materials science, the idea was to divert a 5-microsecond-long portion of each of the accelerator's 750-microsecond-long proton pulses to a tantalum target, producing neutrons for scattering experiments. In 1980, an improved tungsten target/moderator/reflector assembly was put in place with a capability of servicing nine instruments. Richard Silver, the present neutron scattering group leader, oversees both in-house and visiting researchers.

Unfortunately, the WNR has two main drawbacks for neutron scattering, both relating to the time-of-flight style of experiments. Because neutrons come in pulses, researchers can determine the kinetic energy (velocity) and wavelength of a neutron from the time it takes to reach a detector after scattering from a sample. While time-of-flight techniques make effective use of all the neutrons, achieving a high experimental resolution depends on having a sharp initial neutron pulse to represent time-zero in the measurement. It also depends on having a long flight time, which means a long flight path, so that small energy differences show up as measurable time differences. The WNR originally had the broad pulse already described and a small experimental hall, whose longest flight path is 13 meters.

As it happened, the researchers doing the defense-related research also preferred a sharper neutron pulse than available from the WNR, and the laboratory was able to obtain funding from the defense side of DOE (Office of Military Applications) to build the PSR. Instead of taking part of each LAMPF pulse, the PSR takes one entire pulse in every 10. Since it takes less than a microsecond for protons to make one revolution, the effect is to compress the long pulse in time by stacking sections of the pulse one on top of the other as it is fed into the PSR. The end result is to produce a short pulse (0.27 microsecond) of high peak intensity, which is also ideal for neutron scattering.

As it turned out, the WNR/PSR would only be needed a small fraction of the time (20 percent) for defense-related research. Los Alamos officials began talking up the possibility of establishing a national neutron scattering center based on the 80 percent availability of a world-class pulsed source. While funding for the PSR was being sought, an ad hoc panel headed by William Brinkman (now at Sandia National Laboratories) was set up in 1980 by DOE's civilian side (Office of Energy Research) to recommend what neutron scattering facilities it should fund under the assumption that there would be no budget increases.

Pulsed sources use proton accelerators rather than reactors to generate neutrons.

The panel concluded that the reactor-based facilities were the mainstays of the national program and must not only be continued but expanded. The only way to stay in the pulsed neutron scattering game, it decided, was to shut down the IPNS and concentrate on the facility at Los Alamos made available by the weapons program.

This availability did not constitute quite the free ride it might have seemed, however. DOE's defense side did not need and was not going to pay for the enlarged experimental hall, the improved instrumentation, and the space for offices, sample preparation, and computers that would be appropriate for a national user facility. This point was recognized 2 years later by a second panel, also headed by Brinkman, that emphasized that the prior recommendation to focus pulsed neutron research at Los Alamos was based on the assumption that funding from DOE's civilian side for the hall and instrumentation would be available.

All in all, progress at Los Alamos has been slower than neutron scatterers would like it to be because of the failure to obtain funding up to now for the experimental hall and for instrument development. When the WNR/PSR opens for research this fall, there will be five instruments available, mostly those previously used on the WNR or upgraded versions of those. One new instrument, a small angle scattering diffractometer for investigating the structure of metallurgical and polymer materials, is being developed with the aid of laboratory director discretionary funds.

Silver estimates that, with the requested funding, about two instruments per year could be brought on line, so that ten could be available to users about the time the experimental hall would be completed. However, based on the experience at the IPNS, it will probably take up to 3 years to iron out all the bugs in the new instruments. The hall itself would allow for flight paths up to 50 meters in length and would accommodate more than 17 instruments.

The schedule for commissioning the WNR/PSR calls for the first neutrons by this summer and stable operation at one-tenth the design intensity in the fall. Machine development and experiments would then go in parallel, while the intensity is gradually increased to the full value by the fall of next year. The gradual commissioning process is necessary to avoid damage or radioactivity in the PSR due to loss of protons from the beam until machine operators learn how to avoid such losses.

In sum, Los Alamos can carry out productive neutron scattering research with the WNR/PSR without the experimental hall and with a slower pace of instrument development, according to John Browne, the laboratory's associate director for experimental physics. But it will not be the kind of place with the equipment, services, and conveniences necessary for a national user facility of the type necessary to build a following for pulsed neutron scattering.

—ARTHUR L. ROBINSON

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