Research in Progress

Missing Mass

MISSING MASS. Non-luminous matter. Dark halo.

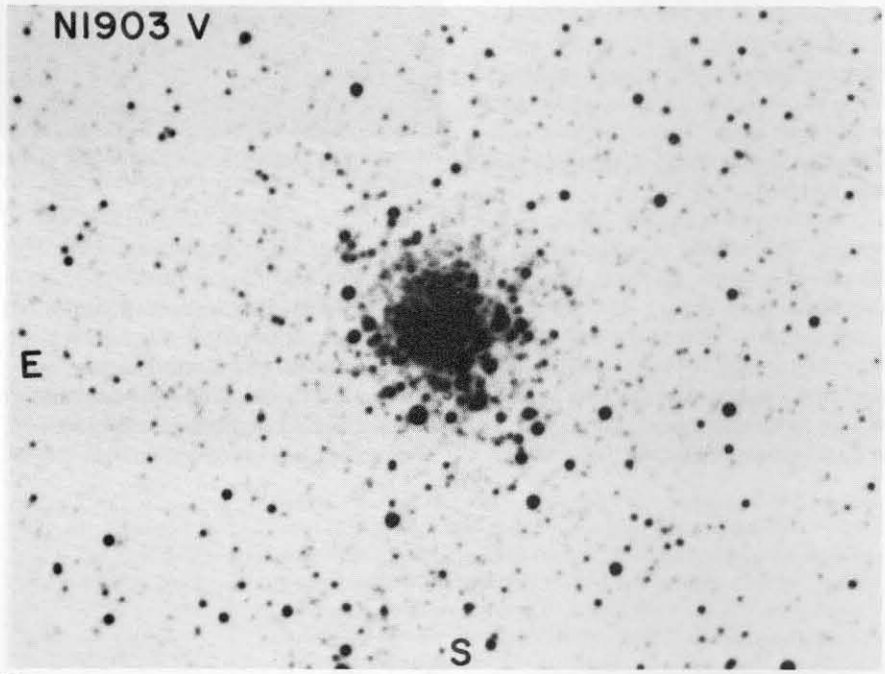
These terms all apply to an intriguing problem uncovered by astronomers in recent years. They have found that all the matter in a galaxy is not accounted for by its stars alone. The mass in a galaxy actually extends far beyond its bright outer edge. How far beyond is a question being pursued by several Caltech astronomers.

Although this mysterious mass can't be seen, its gravitational influence on visible objects is observable. Stars and clusters of stars orbit about the center of our galaxy. Those confined to the disk of the galaxy follow roughly circular paths; those that fill out the galaxy's spherical halo travel in more eccentric orbits, plunging through the disk and back out again on their million-year circuits.

Stellar orbits are controlled by the mass in a galaxy and its distribution. Even though some of the mass doesn't shine, its presence can be inferred through the motions of the stars. Recent doctoral recipient Abhijit Saha used this approach to examine the Milky Way's dark matter.

With Palomar Observatory's telescopes, Saha searched selected sky fields for RR Lyrae stars, rhythmically pulsing stars whose light variations can be used to deduce their distance. And because they are bright, RR Lyraes can be detected even when far out in the Milky Way's halo.

For such distant objects it's only possible to measure the line-of-sight component of their orbits from shifts in the positions of spectral features. This component could be a large part of the total motion for plunging, radial orbits, or a small part if the orbit was more circular. Knowing that the actual orbits



This globular cluster is one of many in the Magellanic Clouds, which contain the nearest dwarf galaxies. Measurement of the motion of globular clusters leads to an estimate of a galaxy's mass.

fell between the extremes, Saha examined the average motions of these RR Lyraes with the idea that the faster they are moving around, the more mass is required to confine them. In this way he showed that the Milky Way's mass extends at least ten kiloparsecs, or 30,000 light-years, beyond the visible outer edge.

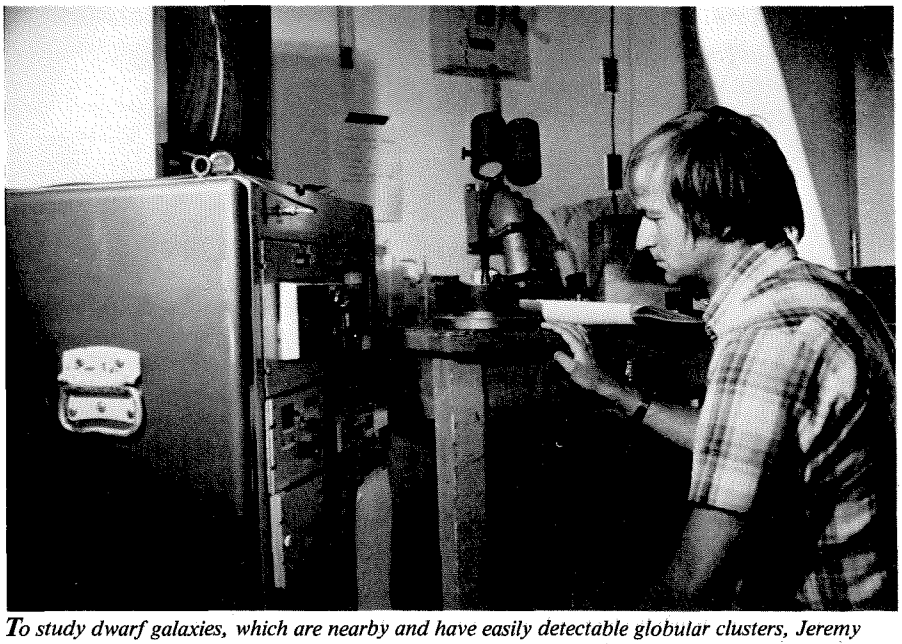
Saha's findings neatly corroborate a 1978 study by F.D.A. Hartwick of the University of Vancouver, and Wallace Sargent, Caltech's Ira S. Bowen Professor of Astronomy. Their study examined the motions of globular clusters about the Milky Way. These dense, compact stellar systems spend most of their orbit far out in the galactic halo and so are a good indicator of distant conditions. Hartwick and Sargent found that our galaxy's mass extends as much as 45 kiloparsecs, or 150,000 light-years, past its nominal outer edge and contains two to four times as much matter as previously thought.

More recently, Sargent has been trying this method to estimate the size of the dark halo around Andromeda, our nearest, full-sized galactic neighbor. His problem so far has been isolating the globular clusters for study. At Andromeda's distance, the clusters, although bright enough to be seen easily, cannot be distinguished from individual stars except in a large telescope. Unfortunately, it would take too long to scan all the outer regions of Andromeda through a large telescope. Instead, Sargent has used Palomar's 48-inch Schmidt telescope to take wide-field photographic

plates. To analyze the plates, he has enlisted the help of a researcher in England who recently devised an automatic plate-scanner. More sensitive than the human eye, the scanner can discern images that appear slightly non-stellar and are potential clusters around Andromeda.

Once a catalog of clusters has been compiled, Sargent will begin a more detailed study, probably similar in method to Associate Professor of Astronomy Jeremy Mould's current efforts. Mould also uses the motions of globular clusters to delineate the dark matter in a galaxy, but he has no trouble discerning the clusters. Mould is studying dwarf galaxies, miniatures of a size between a globular cluster and the Milky Way. Since dwarf galaxies are small, they must be nearby to be seen; at these distances, their globular clusters are easily detected.

Even though the clusters can be detected, their individual stellar members cannot be easily resolved. Mould has been using Palomar's Hale Telescope to create spectra from the overall light of the clusters, from which he will derive their line-of-sight velocities. This in turn will lead to an estimate of the mass of the dwarf galaxy, including the mass that doesn't shine.



To study dwarf galaxies, which are nearby and have easily detectable globular clusters, Jeremy Mould uses the data recording system of the CCD (charge-coupled device) camera at Palomar Observatory. The picture is displayed a few seconds after it has been taken.

Ultimately these investigations of unseen matter could provide information important to a number of astronomical studies. The most dramatic among them is perhaps the critical cosmological question of whether the universe is open or closed, that is, whether there is enough matter to gravitationally halt and reverse the universe's expansion. The final fate of the universe may be determined by the dark, unseen matter that astronomers have only recently become aware of.□ — *John Gustafson*

Improving on Nature

THE MOST commonly used antibiotics are produced in nature — by plants, by fungi, by bacteria. There are plenty of other natural products that are of potential therapeutic value to man, but whose toxicity outweighs their benefit. Actually, anything poison to us is also potentially useful simply because it interacts with the human body, according to Robert Ireland, professor of organic chemistry. The trick is to modify the chemical structure so as to maintain the biological action while diminishing the potency of the toxin. In a way, it is the fine tuning of a biological response through chemical modifications.

Ireland's research involves the synthesis of natural products of potential therapeutic value. The goal of such synthesis is not simply to make more of a particular substance but to be able to change the chemistry slightly and make a molecule better than the one that nature has produced. With any particular molecule the ultimate aim is to broaden the critical gap (called the therapeutic dose range) between the amount of a drug necessary to be effective and the amount that will kill you. "If we can make it, we can change it," Ireland says. He compares his procedures to planning a drive from Los Angeles to New York by the most direct route; then, while actually driving, adjusting the route slightly to end up in Philadelphia.

Since Ireland and his group are interested in the science of synthesis rather than just building better drugs, an essential criterion of a candidate molecule is that it be a complex and challenging problem. His "building block" approach to the problem involves first designing a multistage synthesis strategy — figuring out the components (the building blocks or synthetic intermediates) into which the molecule might be broken and then put back together most efficiently (planning the most direct route to New York). The second stage consists of developing the reaction pathways to reassemble the pieces with slight modifications (because you'd rather be in Philadelphia).

Some of the Caltech chemist's recent work has concerned a biologically important molecule called X537A (also known as lasalocid A). Currently it's used as an additive in chicken feed to

combat coccidiosis, a common infection in chickens. It's also, however, a powerful stimulator of the human heart muscle. The trouble with it is the narrow gap between effective dose and lethal dose — a little bit could either cure you or kill you.

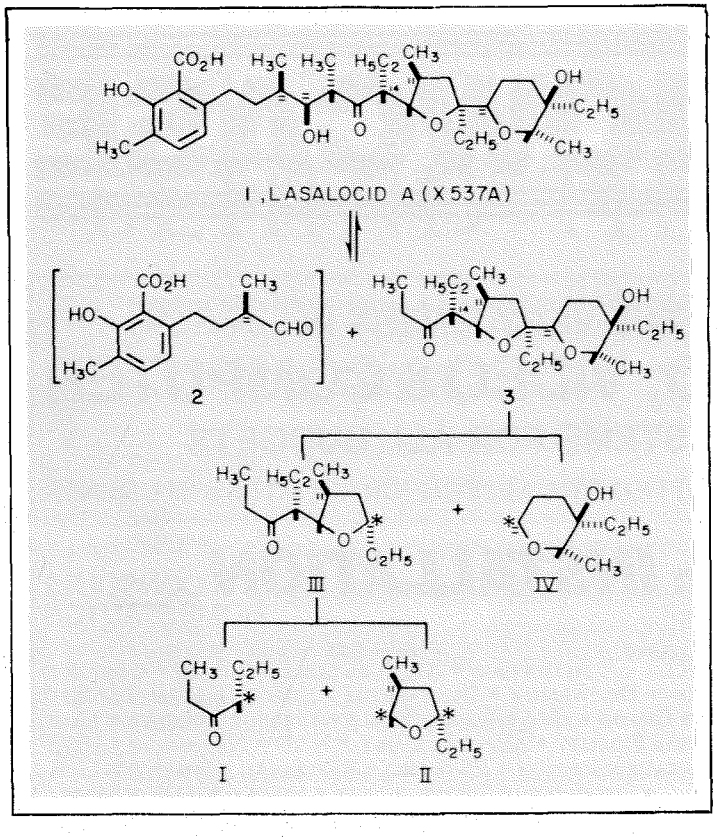
X537A is a polyether ionophore, a group of antibiotics that facilitate the transport of ions across the cell membrane. They do this by surrounding a cation, which is lipophobic, and providing a lipophilic shield, so that the complex can ooze easily through the cell membrane. In the case of the X537A complex, two molecules link together to form a ball around a calcium ion.

Ionophores such as X537A, like most all antibiotics and most other biological molecules in general, are optically active; that is, they are asymmetric in such a way (either left handed or right handed) that they will rotate the plane of polarized light either to the left or to the right. Most antibiotics are dependent on this chirality, or handedness, for their activity; they have to be able to recognize the correct fit with the asymmetric shape of another molecule. It's like shaking hands, says Ireland; if you try to shake someone's left hand with your right hand, nothing fits.

But the theory of ionophore action suggested that even though the X537A-Ca^{+2} complex is indeed chiral and the cell membrane is also chiral, their interaction (and hence transport through the membrane) is achiral — the handedness doesn't matter. X537A exists in nature only in the right-handed form, so to test this theory Ireland and his group have recently accomplished total synthesis of left-handed X537A, made with slight modifications after their successful design for synthesis of natural X537A. Biological testing has proved the theory correct — both left-handed and right-handed X537A molecules have the same biological activity. This achirality makes the drug unique among antibiotics and potentially extremely valuable. Analogs that could widen the drug's therapeutic dose range may be easier to synthesize when a molecule's handedness can be ignored.

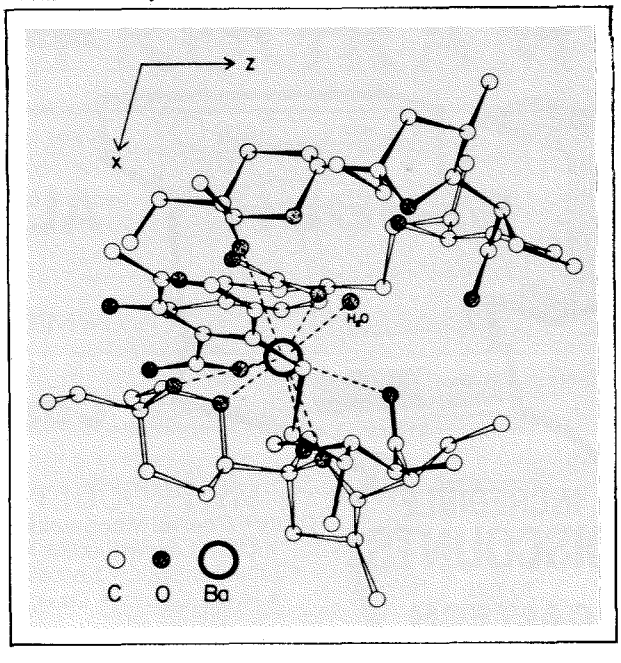
This assumption, as well as Ireland's synthesis strategy for X537A, can be adapted to other ionophores with even more complex structures, such as the molecule monensin. Monensin, however, presents another difficulty that makes its synthesis and modification a very sticky problem. Where other ionophores have a hydrophilic (lipophobic) "inside" to bind to the cation and a hydrophobic (lipophilic) "outside" to ooze through the cell membrane, the monensin-cation complex still has one of its hydrophobic oxygens on the outside, impeding transport. This imperfect structure occurs because nature is restricted to a small set of starting molecules. Chemists, however, are not, and once they can synthesize natural monensin, they can change the starting materials to form a "better" molecule than nature did. Ireland is currently trying to develop a monensin-like structure that has a lipophilic carbon atom in place of the outside lipophobic oxygen of natural monensin.

Among other molecules Ireland is working on are aplysiatoxin (a marine toxin) and streptolydigin (a potent antibiotic). This portion of Ireland's research is funded by the Public Health Service, the National Heart and Lung Institute, and the Hoffmann-La Roche Foundation.□—*JD*



J. Am. Chem. Soc., 1980, 102, p. 1155

In the figure at left, the top configuration represents the structure of X537A, which is broken down below it into synthetic intermediates, or "building blocks." Below is a three-dimensional drawing of two molecules of X537A surrounding a barium ion (similar to calcium) to form a complex with a lipophilic exterior. Reprinted with permission from the Journal of the American Chemical Society.



J. Am. Chem. Soc., 1970, 92, p. 4430