who will enable these projects to be carried out," says Longair. Ostriker echoes his point: "It is important that *groups* be able to submit proposals for large blocks of time. It's going to require a change of style. Astronomers will have to change their mode of operation from that of 'one lone scientist' to that of working in large teams, like the physicists who work on the big accelerators."

Ironically, there is another time allocation issue, just the inverse of the first. It would be very easy to get Space Telescope locked up heel and toe with absolutely first-rate projects—all based on the conventional wisdom. But occasionally, astronomers *do* shout Eureka! So how does one allow for serendipity?

As a partial answer, Giacconi intends to reserve some small amount of Space Telescope's time for the director's discretion. The time would mostly be used for unscheduled events such as a comet or supernova. In fact, says Giacconi, the institute plans to prepare standard observing sequences for such events, so that the staff could implement them quickly and automatically. But this time could also give leeway for offbeat ideas that otherwise might never make it past peer review.

Perhaps a more important approach to serendipity, however, is Space Telescope's ability to operate with at least two instruments simultaneously. While the photometer is taking data, for example, the operators can simply open the shutter of, say, the Wide Field/Planetary Camera and pull in a huge chunk of sky for free. (It is worth noting that on the x-ray satellite Einstein, such wide field exposures led to the serendipitous discovery of a large class of x-ray quasars.) "Many of us think that these will be the most *fun* pictures," says James Westphal of the California Institute of Technology, principal investigator of the Wide Field/Planetary Camera.

Wisconsin's Code imagines this as a new stronghold for the classic lone observer: prowling the Space Telescope archives for unexpected treasures located just to the side of someone else's target. Of course, to prowl the archives one must first *have* the archives, which points up something else about Space Telescope: the science institute is going to be the first observatory to try to keep *all* the data, every binary bit of it.

"It's going to revolutionize the way astronomy is done," says Ostriker, "because right now we throw away 99 percent of the data received on a plate. People end up looking at the same area over and over again because it's easier."

"Archiving and *retrieval*," agrees Code "—it's one of the most exciting new things about Space Telescope." People have been filing away photographic plates in plate vaults for years, he points out, but rarely is there an efficient way for someone else to get at them again. "Then as we started to get digital data with vidicons and CCD's," he says, "the number of bits outstripped the storage facilities. It's only recently that we've had media [high-density magnetic tape and now optical disks] that could store this data in a compact way."

The trick is thus to combine this storage technology with retrieval software that can find the data and get it into a form that someone can use. The problem is not unique to Space Telescope, says Code, but it has been most crucially recognized with Space Telescope. And in this, as in so much else, the Space Telescope Science Institute has taken the lead.—**M. MITCHELL WALDROP**

Next: The Space Telescope Science Institute.

Surviving Heat Shock and Other Stresses

Heat shock genes and their protein products help to protect cells against damage induced by stress and also aid studies of gene control

When fruit flies are exposed to a heat shock they shut off the synthesis of most cellular proteins and turn on the production of a specific constellation of seven heat shock proteins. This response, which appears to protect against the deleterious effects of high temperatures, was once thought to be more or less peculiar to fruit flies. But recent research indicates that it is probably a property of all species. Moreover, many other types of stress also evoke the synthesis of heat shock proteins, suggesting that they may play a more general role in guarding against cell damage.

In addition to shedding light on cells' responses to stresses, studies of the heat shock system are proving valuable for understanding how genes are turned on and off. For example, investigators have identified a nucleotide sequence near the beginning of the genes that is required for the heat shock response.

Although the heat shock response in the fruit fly (*Drosophila*) was discovered some 20 years ago by Feruccio Ritossa at the Laboratoria Internationale Genetica e Biophysica in Naples, current interest in the research began only about 5 years ago. At that time, investigators in several laboratories began to discover that a wide variety of species responded to heat shock in ways that closely resembled the response in the fruit fly.

The organisms displaying the response include the bacterium *Escherichia coli*, unicellular nucleated species such as yeast, the cellular slime mold *Dictyostelium discoideum*, complex plants such as the soybean, and even the cells of mammals and birds. "We recognized that virtually every cell, whatever its source, has a regulatory mechanism at the genetic level that enables it to respond to stresses," says Milton Schlesinger of the Washington University School of Medicine.

Temperatures above 30°C induce a heat shock response in those species, such as the fruit fly and soybean, which normally live at ambient temperatures in the vicinity of 25°C. For the cells of warm-blooded animals temperatures from 42° to 45°C are used to induce the response experimentally.

At roughly the same time that the universality of the heat shock response was becoming apparent, investigators also learned that other types of stresses and agents could evoke the synthesis of heat shock proteins in this whole spectrum of organisms. "We don't think of them so much as heat shock proteins as stress proteins," explains Lawrence Hightower of the University of Connecticut (Storrs), "because there is such a variety of inducers." These inducers include heavy metals, ethyl alcohol, sulfhydryl reagents, amino acid analogs, viral infections, and oxygen deprivation. In mammals, fever may evoke the heat shock response.

Accumulation of the heat shock proteins appears to protect against cellular damage that might be produced by these stresses. Exposing cells for short periods of time to increased, but nonlethal, temperatures can induce thermotolerance in them, enabling them to survive subsequent exposure to otherwise lethal temperatures. Moreover, other treatments that induce the proteins also induce thermotolerance. And, says Gloria Li of the University of California School of Medicine in San Francisco, "The kinetics of thermotolerance development correlates very well with heat shock protein synthesis."

Still missing from the heat shock response picture is a good explanation for the apparent protective effects of the proteins, although there is some evidence that their role may be structural rather than enzymatic. Heat shock proteins may bind to important cellular components and protect them from denaturation or degradation. In particular, they may protect the genetic material.

The proteins have been found in the nucleus, sometimes in association with chromosomes. For example, Joe Key of the University of Georgia has shown that at 41°C the heat shock proteins of the soybean are primarily concentrated in the nucleus and are associated with such subcellular particles as ribosomes and mitochondria. When the temperature is lowered to 28°C, the proteins move into the cytoplasm, but they move back into the nucleus and other structures if the temperature is raised again.

Susan Lindquist and her colleagues at the University of Chicago also find that heat shock proteins are concentrated in the nucleus, where they bind to RNA and chromosomes. In particular, they bind to regions where the chromatin (the complex of protein, RNA, and DNA of which chromosomes are composed) is in its looser, uncondensed state. Transcription of DNA to messenger RNA (mRNA), the first step in protein synthesis, apparently occurs in the areas of unwound chromatin.

Lindquist proposes that heat shock protein binding serves both to protect the chromatin in those regions during high temperatures and to mark the places where transcription was occurring before the heat shock so that they are ready for transcription to resume when the temperature is lowered. "The proteins may be acting as bookmarks and as protective agents as well," she says. However, binding of the heat shock proteins to chromatin is not needed for the second component of the heat shock response, the turning off of the synthesis of other cellular proteins.

Studies of the structures of the heat shock genes and proteins provide another indication that the role of the proteins may be structural. Elizabeth Craig and Thomas Ingolia of the University of Wisconsin in Madison determined the nucleotide sequences of the genes for the four small *Drosophila* proteins, which range in molecular weight from 22,000 to 27,000. (The other three proteins have molecular weights of 83,000, 70,000, and 68,000. The various proteins are designated by the initials hsp, for heat shock protein, plus the first two digits of their molecular weights.) The amino acid sequences deduced from the gene sequences of the smaller genes revealed an extensive region of homology in the proteins, which extends roughly from amino acid 85 to 195 (of a total of about 200 amino acids).

The amino acid sequences of the homologous regions closely resemble that of α-crystallin, a structural protein of the lens of the eye, Craig and Ingolia find. Molecules of α-crystallin form large aggregates, and the investigators postulate that the conserved region may facilitate aggregation of the heat shock proteins to form complexes that might help to stabilize and protect DNA or other cellular constituents.

Not all heat shock proteins are localized primarily in the nucleus, however. According to the Schlesinger group, the large heat shock protein of the chicken is located in the cytoplasm, whereas hsp70 and hsp24 are associated with the filaments of the cell skeleton in the nuclear and cytoplasmic compartments.

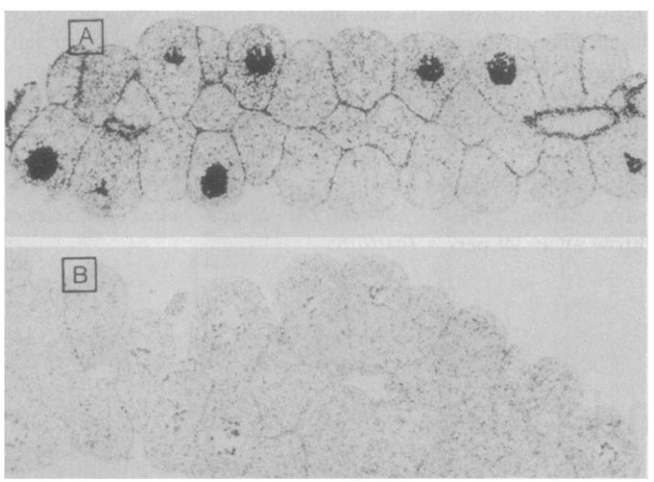
One of the more striking findings is the high degree of conservation of heat shock proteins and genes throughout evolutionary history. The Schlesinger group showed that antibodies against hsp70 and hsp89 of the chicken cross-react with proteins with similar molecular weights from other organisms ranging from yeast to man. Moreover, Craig found 50 percent homology between the *Drosophila* gene for hsp70 and the dnaK gene of *E. coli*, which codes for a bacterial heat shock protein with a molecular weight of 70,000. Craig says, "It is very unusual to show this kind of homology between a gene of bacteria and one from a higher organism."

The heat shock genes of higher organisms resemble bacterial genes in another, more general, way. Most of the heat shock genes studied thus far lack introns, noncoding DNA sequences that are interspersed between the protein coding segments. Introns are not present in bacterial genes but are a feature of most genes of higher organisms.

Using cloned heat shock genes as probes, investigators showed that the genes are members of large multigene families. In *Drosophila*, for example, there are at least three families. One includes hsp68 and hsp70, the second contains the four low molecular weight proteins, and hsp83 belongs to the third. The Key group detected four different families in the soybean, which contain a total of more than 20 genes. Yeast contains about 10 genes related to that of hsp70 of *Drosophila*. "The indication is that we have just scratched the surface of the number of genes in higher species," Craig asserts.

Some members of the heat shock gene families are not activated by a temperature increase, according to Craig. The products of these genes, which she calls hsp cognate genes, may be involved in normal development, as their expression in the fruit fly can vary with developmental stage. In yeast, induction of the heat shock genes occurs during sporulation and may contribute to the thermotolerance of the spores.

Two of the *Drosophila* hsp cognate genes have introns. None has been found



Susan Lindquist/*Cell*, vol. 20, No. 3

Distribution of heat shock proteins

In heat-shocked cells of the fruit fly salivary gland (A), the proteins (dark grains) are concentrated in the cell nuclei and to a lesser extent at the cell membranes. Micrograph B shows normal, unshocked salivary gland tissue.

in a third, but its entire sequence has not yet been analyzed. Otherwise, the cognates are about 75 percent homologous to hsp70.

The role of the cognates is no clearer than that of the heat shock genes themselves. But heat shock can disrupt development in the fruit fly. Herschel Mitchell of the California Institute of Technology says, "You can get a great variety of abnormalities. Many resemble known mutants." The type of abnormality depends on the time during development at which the shock is applied.

The structural aberrations are apparently caused by the disruption in normal gene expression that heat shock produces. Mitchell hopes to unravel the biochemical basis of the induced abnormalities, and possibly of the corresponding ones which are caused by mutations, by determining what specific changes in gene expression are correlated with the observed abnormalities.

Heat shock activates synthesis of the proteins by turning on transcription of the genes into mRNA. Consequently, the response is very useful for studying the control of gene expression.

Because of the simplicity of the bacterial system, analysis of heat shock gene control in *E. coli* is especially advanced, even though the response in this organism is among the more recently discovered. A similar picture of the control has emerged from studies in Frederick Neidhardt's laboratory at the University of Michigan and that of Takashi Yura at Kyoto University.

During the middle to late 1970's, when the Neidhardt group was studying certain temperature-sensitive mutants of *E. coli*, they noted major changes—both increases and decreases—in protein synthesis, even in the normal controls. In particular, the synthesis of a group of 14 proteins increased.

"The critical discovery came," Neidhardt explains "when we looked at a mutant isolated by Stephen Cooper [of the University of Michigan]. None of the high-temperature proteins were induced in the mutant." The mutant cells die when maintained at 42°C, a temperature that does not normally kill *E. coli*.

The mutation responsible for the lost response turned out to be in a regulatory gene that controls the synthesis of all 14 proteins. The genes for these proteins constitute a regulon—a group of genes which are scattered throughout the genome but are controlled together.

The Neidhardt group has identified a protein with a molecular weight of 33,000 as the product of the regulatory gene. "It is a positive regulator. Its presence is necessary for induction of this HTP [high-temperature protein] regulon," he says.

Neidhardt and his colleagues have also determined the identities of 4 of the 14 proteins. One is the product of the dnaK gene, which is 50 percent homologous to the hsp70 gene of *Drosophila*. The dnaK gene product is necessary for initiation of the synthesis of phage (bacterial virus) DNA. Its role in the uninfected cell is unknown. Two of the proteins are products of genes necessary for steps in the assembly of phage particles, but they are needed for bacterial growth as well. And the fourth gene codes for one of the enzymes that attach the amino acid lysine to transfer RNA.

Control of heat shock gene transcription in higher organisms has been studied mainly in gene transfer experiments. Cloned genes from *Drosophila* have been introduced into foreign cells, including mouse and monkey cells and frog oocytes. The transferred genes are not only transcribed there, but the transcription is activated by heat shock, according to investigators in the laboratories of Mathew Meselson of Harvard University, Hugh Pelham of the MRC Laboratory of Molecular Biology in Cambridge, England, and Alfred Tissières of the University of Geneva. This suggests that the mechanisms for transcription control have been highly conserved during evolution.

"The proteins may be acting as bookmarks and as protective agents as well."

The DNA sequences required for appropriate regulation of transcription generally lie just before the beginning of the gene segments that code for protein structure. By systematically deleting DNA segments in and around that region before transferring the cloned genes, the investigators have identified a short sequence that is necessary for the usual heat shock response. The sequence extends roughly from nucleotide −50 to nucleotide −65, counting backward from the initiation site for transcription of the heat shock messenger.

Comparisons of the nucleotide sequences in that region of several *Drosophila* heat shock genes have revealed a conserved region of about 14 nucleotides. This consensus sequence is about 25 nucleotides upstream from the TATA box sequence, which is necessary for accurate initiation of transcription in nucleated cells. The TATA box and the consensus sequence apparently interact to give accurate initiation of transcription in response to heat shock. Putting the consensus sequence in the appropriate location near a gene that is not normally inducible by heat confers that response on it.

There is some uncertainty about the exact function of the consensus sequence, however. Pelham notes, "We all agree on the boundaries of the consensus sequence. There is a slight disagreement about whether they [heat shock genes] become constitutive when you delete that sequence." Meselson and Victor Corces, who is now at Johns Hopkins University, find that after deletion of the consensus sequence, expression of the gene becomes constitutive—that is, the mRNA is made all the time, although in low concentrations. Meanwhile, Pelham finds that the product is not made at all when the consensus sequence is deleted. The two groups used different methods for introducing the cloned heat shock gene and this may account for the discrepancy.

Finally, when the temperature is lowered, heat-shocked cells eventually revert to their normal patterns of protein synthesis. According to Lindquist, the reversal differs significantly from the original response. Restoration of normal protein synthesis is slower, for example. In addition, when heat shock represses normal protein synthesis in the fruit fly, the messengers are sequestered rather than destroyed. But in the reversal of the heat shock response, the heat shock messengers are degraded.

The Lindquist group finds that accumulation of functional hsp70 is required for this degradation to occur. Accumulation of the protein also blocks further transcription of heat shock genes into mRNA. The net effect is that production of the proteins is self-regulated; the proteins turn off their own synthesis when the cell accumulates the amount appropriate to the degree of stress that initiated the response.

Heat shock proteins are also needed for release of the translation block of the lower temperature messengers of *Drosophila*. Eventually, with the stress over and the cellular machinery having been protected by the heat shock proteins, the cell can return to normal life.

—JEAN L. MARX

Additional Reading

The proceedings of a symposium on heat shock proteins, which was held at Cold Spring Harbor Laboratory on 5 to 9 May 1982, were published in *Heat Shock: From Bacteria to Man*, M. J. Schlesinger, M. Ashburner, A. Tissières, Eds. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1982).