Drug Found to Help Heart Attack Survivors

An NHLBI study of propranolol was ended early because the drug so clearly prolonged the lives of heart attack patients

On 29 October, the National Heart, Lung, and Blood Institute (NHLBI) announced that it was ending its Beta-Blocker Heart Attack Trial 9 months ahead of schedule because the results were so good. The study's data monitoring committee determined that it would be unethical to continue giving half of the study's participants placebos, rather than propranolol, the drug being tested. The study showed that heart attack patients who take propranolol significantly improve their chances for survival.

About 1,250,000 persons have heart attacks each year in this country. Of them, 350,000 survive. If propranolol came into widespread use, at least 6500 lives would be saved each year in the United States alone, according to NHLBI estimates.

The study involved 3837 heart attack victims between the ages of 30 and 69. All were enrolled in the study between 5 and 21 days after their attacks and were randomly assigned to take propranolol or placebo. After 2 years of follow-up, 9.5 percent of the propranolol group have died but only 7.0 percent of the placebo group have died. The propranolol group had 26 percent fewer deaths. And all patients in the trial seemed equally responsive to the drug. "The effect is present independent of age, sex, or race, independent of the part of the heart involved and independent of the severity of the heart attack," said ebullient Peter Frommer, who is acting director of the NHLBI.

Propranolol, which is frequently prescribed to lower blood pressure or relieve angina pectoris, is already one of the most widely used drugs in this country. It is one of a class of drugs called beta-blockers that blocks beta-adrenergic receptors on heart cells. These receptors bind hormones secreted by the sympathetic nervous system in response to stress or excitement. Once the hormones bind, the heart beats faster. By blocking beta-receptors, propranolol reduces the amount of work done by the heart.

William Friedewald, who is associate director for clinical applications and prevention at the NHLBI, cautions that no one yet knows why propranolol increases the survival rate of heart patients. It may prevent further heart attacks or it may prevent sudden death from ventricular fibrillation, which occurs when heart muscle cells start to contract continuously but asynchronously so that there is no effective heartbeat. (Friedewald describes a heart in ventricular fibrillation as looking like a lot of worms wriggling on the surface.) Some answers may be forthcoming when the NHLBI study investigators analyze their data on the causes of death among the trial participants.

The NHLBI decided, in 1975, to test propranolol in heart attack patients for two reasons. First were the results of animal studies done 15 years ago. Investigators cut nerves going to the animals' hearts and found that the animals then did not have ventricular fibrillations when a heart attack was induced. By preventing nerves from acting on the heart, propranolol might have a similar action. The second reason why the NHLBI focused on propranolol was that the drug had been given to patients in 6 small-scale studies with results that, although not conclusive, hinted that it would be of some benefit to heart attack patients.

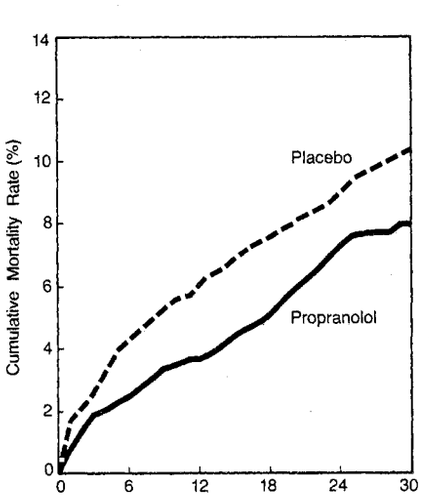
The propranolol study is the third NHLBI study of drugs that it was hoped would improve the survival rates of heart attack patients—and the only one with positive results. In the mid-1960's, the institute began a study of five cholesterol-lowering drugs. Investigators soon discovered that not only were these drugs ineffective in prolonging the lives of heart attack patients but three of them were so toxic that they had to be dropped from the study altogether. In the early 1970's, the NHLBI tested aspirin, which it thought might help prevent further heart attacks by stopping blood clots from forming in coronary arteries. The results of the aspirin trial were inconclusive; the drug had no clear beneficial effect.

Until now, cardiologists had no proven drug for heart attack patients to prolong survival. Nonetheless, some doctors were prescribing propranolol anyway. "That was one of the problems we had in recruiting for this trial—doctors were already giving patients propranolol," says Friedewald.

The results of the NHLBI propranolol study are consistent with results of two European studies reported earlier this year. In Norway, the beta-blocker timolol was found to lower the mortality rate of heart attack patients and in Sweden another beta-blocker, metoprolol, had a similar effect. Metoprolol, but not timolol, is available in this country.

Propranolol, as well as other beta-blockers, can cause side effects, including low blood pressure, fatigue, faintness, depression, and gastrointestinal problems. But the number of patients in the NHLBI study who had to discontinue taking propranolol because of these side effects was very small. Only about 1 percent stopped because of low blood pressure, for example. According to Friedewald, most patients who suffer side effects can tolerate a lower dose of propranolol–they need not stop taking the drug. Contraindications include bronchial asthma, serious congestive heart failure, symptomatic low blood pressure, and pulmonary hypotension.

Asked what advice he would give patients with heart disease, Sidney Goldstein of Henry Ford Hospital in Detroit, who is chairman of the propranolol study's steering committee, said, "Our results are clearly geared to people who



Mortality during the propranolol trial

At all times, the treated group did better than those given placebos.

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experienced a recent heart attack. Our recommendation would be that people who had a recent heart attack be started on this drug prior to their discharge from the hospital. We could possibly extrapolate to people 3 months after their heart attack but we do not have the information to deal with the question of whether people should start taking propranolol if they had a heart attack as long as 5 years ago." Goldstein said it was up to doctors' clinical judgment to decide when heart attack patients should stop taking propranolol, if ever.

The results of the propranolol study, Friedewald concludes, "are an exciting breakthrough. Until now, we had nothing for patients who survived a heart attack. Now we have a drug that reduces mortality by 26 percent. That's an astonishing figure."—GINA BARI KOLATA

Genes Regulated Through Chromatin Structure

Unusual areas of chromatin upstream from genes are necessary for gene activity

In the electron microscope, all DNA from cells of higher organisms looks pretty much the same. Sections of the DNA containing active unique sequence genes cannot be told apart from inactive regions of DNA. Yet, clearly, there must be something that distinguishes transcriptionally active regions of DNA and that something, it is becoming apparent, is structure. Molecular biologists are uncovering evidence of structural differences in active regions of DNA and, in particular, are finding an unusual conformation upstream from active genes that appears to be necessary for transcription.

It comes as no surprise that DNA structure is so important for gene activity because DNA in cells of higher organisms is not merely a simple double helix. The DNA is virtually covered with proteins and when spread in electron micrographs, looks like beads on a string—the beads being balls of histone proteins with DNA wrapped around them and the string being DNA with still other proteins attached to it. This complex of DNA and proteins is called chromatin.

But, despite the likelihood that chromatin structure holds clues to gene activity, until very recently only a few molecular biologists focused on it. The problem was a lack of techniques to study gene expression in vivo. What most molecular biologists did was to strip the DNA of its proteins and, using methods that work so well for bacteria, transcribed the DNA in vitro, looking for sequences that may be necessary or sufficient for the regulation of gene expression.

In the opinion of many researchers in the field, the previous development of major significance in studies of chromatin structure occurred about 5 years ago, when investigators tried to solve the beads-on-a-string structure, and quickly succeeded. Since no one knew how to probe chromatin structure any further, they went on to other sorts of experiments. "Structure gets boring without function," explains Harold Weintraub of the Hutchinson Cancer Center in Seattle. Richard Axel of Columbia University agrees. "We're just getting back to chromatin structure. We waited until we knew where on the chromatin to look."

What helped turn many molecular biologists back to chromatin structure was, first, advances in recombinant DNA technology that allow them to pick out specific genes or chromatin regions containing genes, study or even alter the sequence, and then, if desired, reinsert the DNA sections into cells to examine their chromatin structure in vivo. The second impetus to look at chromatin structure was a finding by Weintraub that the enzyme DNAase I can more easily cut active than inactive regions of chromatin. Apparently, transcriptionally active regions of DNA have a more "open" or more "relaxed" structure that makes them more accessible to this enzyme. This was the first evidence that active genes really are structurally distinct.

Using this nuclease, Weintraub and his associates discovered that active globin genes and the chromatin surrounding them in chicken red blood cells are ten times more sensitive to the enzyme than the bulk of transcriptionally inactive chromatin. Inactive globin genes in red blood cell precursors or in brain cells, in contrast, are not particularly sensitive to the enzyme. The sensitive region in the red blood cells contains the globin genes and is about 100,000 bases long; the globin genes themselves are only 1000 to 2000 bases long.

Then, Carl Wu, now at Harvard University, followed by other researchers, began finding hot spots for DNAase I—short stretches, consisting of 100 to 200 nucleotides, that are 100 times more sensitive to the enzyme than are the average stretches of chromatin. These hot spots can show up nearly anywhere, it seems, appearing before genes, after genes, within genes, and even in areas of chromatin where there seem to be no genes at all. But what is most intriguing is that the hot spots that appear in front of genes seem to have a connection with gene activity.

As molecular biologists began looking for these so-called DNAase I hypersensitive regions, they found that every time a gene is active, a hypersensitive region can be found upstream from the gene.

So far, the hypersensitive regions have been found upstream from active chicken globin genes, active rat insulin genes, active yeast genes involved in mating, and a number of active *Drosophila* genes, including several heat shock genes, insulin genes, and a gene coding for glue protein. The hypersensitive regions, moreover, seem to be in a highly unusual conformation. Because hypersensitive regions have been found upstream from such a wide variety of active genes, Sarah Elgin of Washington University concludes, "It is safe to assume that if a gene is capable of being transcribed, it must have a hypersensitive region at its 5′ end."

Having gotten this far, molecular biologists are asking what happens to gene expression if a hypersensitive region is deleted or mutated, when during tissue differentiation do these hypersensitive regions appear, what do the regions look like, and how are the regions related to certain DNA sequences that seem important for gene expression in vitro.

The most dramatic evidence of what happens if a hypersensitive region is deleted comes from work by Mark Muskavitch, now at Harvard University, and Steven Beckendorf at the University of California at Berkeley. Muskavitch isolated *Drosophila* mutants whose larvae do not make glue protein, a protein

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