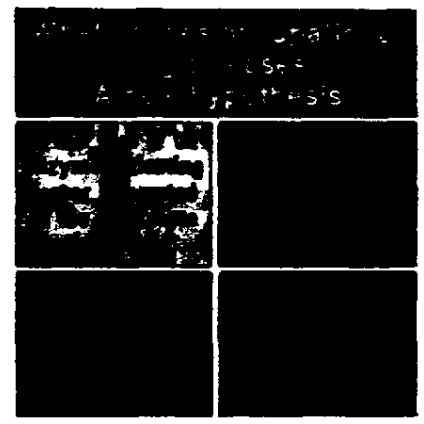
Unlocking the mysteries of respiratory diseases



In a research project on brown lung disease, or byssinosis—an ailment that afflicts many cotton mill employees—a University of Chicago team has found toxins that may prove to be a clue to the general mechanism of numerous respiratory diseases that affect employees in chemical plants and in other industrial settings. Among such occupational maladies: asbestosis, silicosis, black lung disease in coal miners and chronic asthma, which afflicts some workers in the chemical industry (*CW, Sept. 22, 1982, p. 52*).

Furthermore, the study team developed procedures that may be used in pinpointing the agents that cause such diseases. And, of course, if those agents can be found, it may be possible to devise measures to keep them handcuffed.

In the brown lung project, the Chicago study team—headed by Associate Professor David Lynn—has not yet been able to identify a causative agent, but it has found four toxins that were formed, Lynn thinks, by the action of some such agent. He says the toxins were found in the lungs of deceased cotton mill workers, and that he and his co-workers have shown that those compounds were absent, or present only at considerably lower levels, in the lungs from a control group that did not work with cotton.

This is the first study so far to find specific toxins associated with cotton workers, but Lynn cautions that the study was limited. "Our research was aimed at developing techniques to determine the cause of brown lung disease, not proving its association with cotton work," Lynn says. "Nevertheless, our results are dramatic and imply there is an association."

First-stage finding. Washington officials who are concerned with occupational health are aware of the Chicago team's work but regard Lynn's recent report to the American Chemical Society as a first-stage finding. Lynn has yet to show a cause-and-effect relationship between brown lung disease and the four lung toxins he has isolated, says Robert M. Castellan, chief of the clinical section division of respiratory disease studies at the National Institute for Occupational Safety and Health (Morgantown, W. Va.). "It's early in the game," says Castellan, who has heard Lynn present his work. "His work is still preliminary." And while Lynn's work does suggest a possible mechanism by which a variety of environmentally induced lung diseases might develop, in that area, Castellan says, "the cause-and-effect relationship becomes even more tenuous."

Lynn, in a cautionary note, states that his study does not provide conclusive answers to these questions but does provide an important lead in the search for the cause and perhaps eventual prevention of byssinosis. The Chicago researchers say the source of the toxins in the lungs isn't certain, though they have isolated one from cotton and also have found related compounds that could serve as precursors for the other three. In addition, two of the toxins were found in tobacco leaves. As to the validity of the studies, observers say

Toxins found in cotton mill employees may be the key to other industrial maladies

the main limitations were that the sample was too small and the subjects' case histories were too incomplete to make general assumptions tying the toxins to cotton mills. Only seven cotton workers and eight other persons were tested.

A link? Nevertheless, Lynn, who is an associate professor of chemistry, says these results at least point to cotton dust as the cause of byssinosis. "All seven cotton workers had the toxins in their lungs and none of the others had any," he says. "This isn't proof, but it does strongly indicate a link between cotton dust and byssinosis."

The four toxins the Chicago group isolated are all members of a family of compounds called oxidized C_{18} fatty acids. Many compounds of this family are found in nature; in mammals, for example, they serve as precursors for prostaglandins. Lynn theorizes that enzymes, either in cotton or in the lungs, oxidize the C_{18} fatty acids—i.e., acids having 18 carbon atoms in each molecule—to the toxins. "We aren't sure if this occurs in cotton particles, or if there is something in cotton that induces lung enzymes to do the toxin-forming reaction," he says, adding that both may be taking place. If the latter is true, other enzyme-inducing agents might be involved in causing other occupational lung diseases.

Besides trying to answer that question, Lynn's research group is now trying to determine why these compounds accumulate in the lungs of cotton workers; they are found there even years after exposure to cotton dust has ceased. If it turns out that cotton dust contains an enzyme inducer, the compound might permanently turn on these fatty-acid oxidizing enzymes in lung cells. The enzyme might then convert naturally occurring C_{18} fatty acids into toxin molecules. Since the precursor compounds are found in tobacco leaves, they might be widespread throughout nature and be readily available as substrates for the enzyme.

Another theory is that the compounds are formed only while exposure is taking place but that they are incorporated into the cell membranes of lung cells. The cell membranes would then be a toxin reservoir, slowly releasing the compounds over time.

Outcome. Further research will be greatly aided by techniques developed in this study, according to Lynn. "This is the most important outcome of our work," he says. "We now know how to spot the presence of toxins quickly and which four compounds to look for in dust samples and samples from affected subjects. We have all the tools we need to see if a clear link exists between damaging compounds and a history of work in a cotton mill. If a complete study with more subjects reproduces our results, we'll have an answer to this question."

Lynn has synthesized all four toxins in the laboratory, and they will now be tested to see whether they induce a byssinosis-like disease in test animals. "This," he says, "would be compelling evidence that the toxins we found in the cotton workers cause byssinosis." □