THE NEW YORK TIMES **NEW YORK** FRIDAY, FEBRUARY 27, 1998



# *Giuliani Withdraws Financing For Asthma Program in Bronx*

By ESTHER B. FEIN

Mayor Rudolph W. Giuliani said yesterday that the city was withdrawing its money from a multimillion-dollar asthma education and treatment initiative in the Bronx, saying the organization selected to run the program was refusing to agree to the city's plan for financial and program supervision.

The program, which has been championed by Hillary Rodham Clinton, was to have been managed by the Children's Health Fund in conjunction with Montefiore Medical Center in the Bronx. In its 11-year history, the fund has become a national model for providing health care to poor children and its asthma initiative would have cost $2.3 million per year for four years, with the city providing $1.5 million annually and the state providing the remaining $800,000.

Asthma is considered the worst chronic health problem affecting children, and is particularly prevalent among the urban poor because of the lack of accessible health care and the high number of allergens in the environment. If poorly managed, asthma can lead to extensive hospitalization of children and many missed days of school.

The president of the Children's Health Fund, Dr. Irwin Redlener, denied that his organization was balking at sharing its financial and patient records with the city, but said that the requirements being demanded were so onerous that "they threatened to strangle the implementation of the program with a flood of bureaucratic paperwork."

Dr. Redlener, who is also the director of community pediatrics at Montefiore, said the city wanted, for example, monthly financial accountings, approval of treatment plans for every patient, and weekly schedules of doctors' hours. The Children's Health Fund, he said, had offered quarterly reviews of the accounts, patient charts and schedules.

Dr. Redlener said that he was stunned by the Mayor's announcement yesterday at City Hall that the city would no longer help finance the project, adding that he thought his organization and the Health Department had been making progress.

Relations between the city and the Children's Health Fund have been strained almost from the start, with the two sides arguing over what the initiative's focus should be — the city favoring community and physician education and the health fund favoring direct patient care.

Yesterday, city officials and Dr. Redlener both promised to carry on their asthma initiatives independently. Dr. Redlener said that Schering-Plough, a pharmaceutical company based in New Jersey, had pledged $750,000 a year for two years toward the program.

Fred Winters, a spokesman for the city's Health Department, said the city would find another vendor to provide asthma services to Bronx communities. "The money for asthma will not be lost," he said. "It will be redirected."

DAILY NEWS • Friday, February 27, 1998

# Rudy kills 2.3M fund for asthma

By FRANK LOMBARDI and JOE CALDERONE
Daily News Staff Writers

Mayor Giuliani yesterday abruptly canceled funding for a $2.3 million asthma program that First Lady Hillary Rodham Clinton had touted in a visit to the South Bronx last year as a potential national model to combat the disease.

The mayor pulled the plug after the program's president, Dr. Irwin Redlener, complained in an interview with the Daily News that the city Health Department had been dragging its feet on a contract to deliver the asthma services, even though the funds had been set aside months ago.

Giuliani yesterday said Redlener and the Children's Health Fund, which runs the program, were "unwilling to be accountable for spending."

"He has refused to live by the accountability standards that we now have in our health care contracts of all kinds," the mayor said. "Therefore, the Department of Health, on the merits, responsibly decided not to do business with him, and they're not going to do business with him. They are going to have those services provided in other ways."

Redlener yesterday said he was willing to go along with reasonable standards but objected to reporting requirements contained in a 14-page rider that was added to the standard city contract.

"They wanted to approve the purchase of every single piece of equipment in advance," he said.

The fund and the City Council last summer devised a four-year plan to expand asthma education and medical services.

"Enough is enough," said Council Speaker Peter Vallone (D-Queens). "We need to get this money away from the bureaucrats and get it delivered to the thousands of children who are suffering."

The program called for increasing staffing for asthma services at a South Bronx clinic affiliated with Montefiore Medical Center and to provide increased services in Williamsburg, Brooklyn. The fund also planned to dispatch two specially equipped vans to schools and shelters where asthma rates are high.

> ***"Doesn't the mayor realize that people are dying?"***
>
> **MAVELIN MORALES**

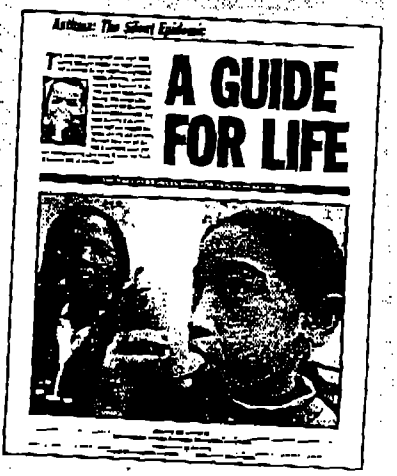
Outside the clinic yesterday, asthma sufferers said they were disappointed with the mayor's decision. "Doesn't the mayor realize that people are dying?" said Mavelin Morales, 37, whose 5-year-old son, Benigno, is treated at the clinic. "They keep putting smokestacks and Dumpsters in this neighborhood but not asthma clinics."

A White House official called the program's demise "unfortunate" but said the First Lady would not take sides.

**COMING SUNDAY**

## Asthma: A Guide for Life

**A special 8-page guide for asthmatics and their families, showing how to detect the symptoms, where to get help and what to do in an emergency.**




Friday, February 27, 1998 • DAILY NEWS

U.S. Department of Health and Human Services
Office of the Regional Director
26 Federal Plaza, Room 3835
New York, New York 10278

# FAX TRANSMISSION NOTICE

DATE: 2/27/98

TO: Melanne Verveer, Office of First Lady FAX Number: (202) 456-6244

ORGANIZATION:

FROM: Alison E. Greene, Regional Director
(212) 264-4600 (phone)
(212) 264-3620 (fax)

NUMBER OF PAGES (including this cover): 2

Please notify us immediately if not received properly. Thank You.

MESSAGE:

This is exactly what I was concerned about last December.

Alison

TO: Hillary Rodham Clinton
FROM: Jennifer Klein
DATE: 11/5/97
RE: The Vice President's Question on Study Linking Increased Asthma and Antibiotic Use

You had asked for information about a study that the Vice President mentioned linking increased asthma and antibiotic use. I have attached two articles discussing a recent study done in Japan that found that increased rates of childhood asthma are related to decreased rates of infectious diseases, such as measles and tuberculosis. The study does not make a direct link between antibiotics and asthma. Instead, it posits that, with better living standards and immunization programs, children have fewer respiratory infections. Childhood respiratory infections stimulate a response in the developing immune system that may protect against asthma. With fewer infections, therefore, children are at greater risk of suffering from asthma.

Experts from the National Institutes of Health, the American Lung Association, and the Asthma and Allergy Foundation of America caution that there are questions about this study. Most research finds that the rise in asthma is related to changes in the environment and to genetic predisposition.

Jen – This note is from VP Gore

THE WHITE HOUSE

WASHINGTON

Please follow up + find study

Did you see

the article in [illegible]

increased [illegible] and childhood

antibiotic use?

The issue is this:

[illegible] antibiotic use

in children (their point is that

life threatening infections are often

contracted) by [illegible]

systems of [illegible] for

"training" and [illegible] development

and "fine tuning." The underlying

"poorly trained" immune system regard

inappropriately [illegible]

TO: Jennifer Klein
FROM: Jon Poling

DATE: November 5, 1997

RE: Relationship Between the Immune System and Atopy (Allergic Response) or Asthma in Children

The following studies suggest that increased rates of childhood asthma are related, in some degree, higher immunization rates and antibiotics use, the diminished exposure to infections and a less independent immune system. Attached are three articles for your review:

- **The Inverse Association Between Tuberculin Responses and Atopic Disorder**
  The study discusses how the increased rates of childhood asthma are related to the deceased rates of Tuberculosis and other infections. I believe that this is the study that we have been looking for and seems to deal with the issue that Vice President Gore had mentioned.

- **Asthma: An Epidemic in the Absence of Infection**
  The article is a complementary piece to the previous study. It summarizes the findings of the previous study and offers an overview with less medical jargon.

- **New Clues to Asthma Therapies**
  The article discusses asthma therapies, but there is another article within this one entitled **Why the Rise in Asthma Cases**, that discusses the relationship between a decrease in infections and an increase in atopy.

Experts who I have talked to from the National Institutes of Health, the American Lung Association, the Asthma and Allergy Foundation of America and other offices all say that this study is very new and has not been thoroughly researched. Furthermore, they tell me that this, if true, is certianly not the only cause for the increase of Asthma cases in developed countries like the United States. Other articles and studies have been written on the increase of Asthma cases being related to genetic and environmental reasons.

I have highlighted specific portions of the text that I think you may want to look over. If you want to read a complete article, I would suggest reading the Asthma: An Epidemic in the Absence of Infection or Why the Rise in Asthma Cases.

# New Clues to Asthma Therapies

**Identification of major players in the inflammatory cascade that damages the lungs in asthma offers targets that may produce better treatments for the disease**

A rising pollen count means itchy eyes, scratchy throats, and stopped-up sinuses for many allergy sufferers, but for those whose allergies trigger asthma, this means more than just discomfort. For them, exposure to usually harmless pollen or other allergens can set off a life-threatening attack in which the airways leading to the lungs close up—making the sufferers feel, they say, as if they are trying to breathe with a full-grown person standing on their chest. These frightening attacks are becoming more and more common. Since 1980, the prevalence of asthma has almost doubled in the United States. Today, it afflicts more than 14 million people in this country alone, and costs almost 5000 lives each year—with no signs of leveling off.

Researchers don't have a clear idea of what is causing this increase (see sidebar). Nor have they worked out what predisposes some people to asthma in the first place. But on one front, they are making real headway. They are beginning to pinpoint many of the key biological players that take part in asthma attacks. And that in turn is providing researchers with openings for new ways to treat asthma, some of which are just entering clinical use. "There is a story that's coming out," says Yale pulmonologist Jack Elias. "It's beginning to hang together."

The main theme of the story is inflammation. Doctors have known for years that asthma attacks are often triggered by allergens, such as cockroaches, dust-mite feces, pollen, or animal hair. Now, researchers are working out the exact cascade of events that these allergens—and other nonallergen triggers such as cold air, viral infections, and exercise—set in motion in the lungs. At the top of the cascade is a particular type of immune cell called the T lymphocyte, which responds to the noxious substances by sending out more than a dozen chemical signals: so-called cytokines, which attract inflammatory cells to the airways of the lungs.

These warriors, in particular those called the eosinophils, release chemical weapons of their own. This second wave of signals, including histamine and small, fatty molecules called leukotrienes, causes blood vessels to leak and lung tissues to swell, contracts the smooth muscles of the airways—cutting off the air supply like squeezing a hose—and encourages mucus production, further clogging already constricted airways. Each crisis causes an immediate difficulty in breathing, and repeated crises over time lead to permanent lung changes that may make the next attack even worse.

Current asthma treatments are aimed at the end result. Bronchodilators open the airways, and antihistamines and steroids reduce inflammation. But by dissecting the chain of command that leads to an attack, researchers have identified a whole new set of promising targets for asthma drugs. "The therapy is moving back closer and closer to the beginning of the inflammation cascade," says Harold Nelson, an allergist and immunologist at the National Jewish Medical and Research Center in Denver. The hope is that these therapies, because of their improved specificity, will be more effective and less liable to cause dangerous side effects than current treatments.

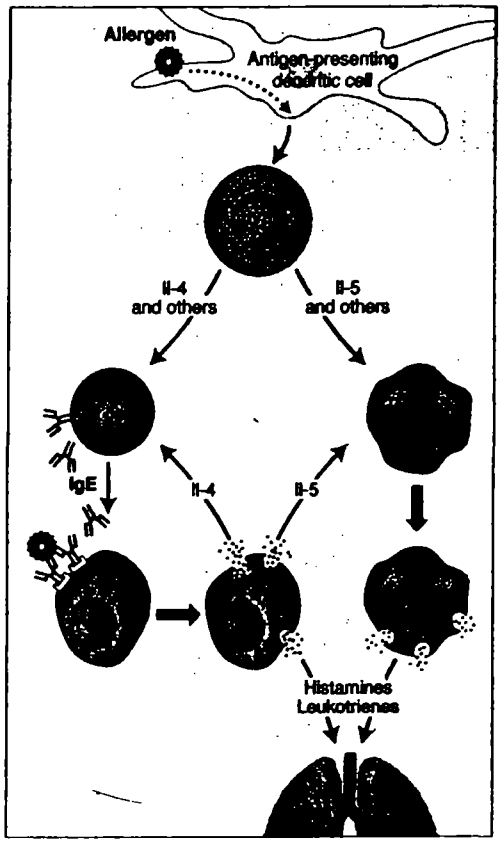



ILLUSTRATION: K. SUTLIFF

**Overzealous warriors.** The T lymphocyte helps command the immune cells—including mast cells and eosinophils—that react to pollen, cold, exercise, and other stimuli to trigger an asthma attack.

Although most of the treatments aimed at the inflammatory cascade are a few years away from patients' medicine cabinets, two have already made it to the shelves. Both drugs, which were approved late last year by the U.S. Food and Drug Administration (FDA), got ahead of the crowd for the simple reason that their targets, the leukotrienes, were implicated in the cascade nearly 50 years ago.

Released by activated eosinophils and other immune-system soldiers recruited to asthmatic lungs, the leukotrienes have several effects that contribute to the airway constriction and inflammation of asthma. They recruit other inflammatory cells, for example. But they are particularly effective in contracting the smooth muscle of the bronchi, the tubes carrying air from the trachea into the lungs. Molecule for molecule, says pulmonologist Jeffrey Drazen of Brigham and Women's Hospital in Boston, the leukotrienes are the most potent bronchoconstrictors ever described—a fact, he adds, "that was not lost on the drug companies," which set out to develop inhibitors.

The two approved last year are Zileuton, which blocks a vital enzyme needed for leukotriene synthesis and is marketed by Abbott Laboratories in Chicago, and Zafirleukast, which blocks the lipid's receptors on smooth muscle and other cells and is produced by Zeneca Pharmaceuticals, based in the United Kingdom. Two more receptor blockers, from Merck and from SmithKline Beecham, are awaiting FDA approval.

The drugs have worked miracles in some hard-to-treat patients, Drazen says. "In some patients it's like manna from heaven. We treated a veterinarian allergic to dogs and cats who was just miserable. On this treatment, he is a normal person again." But for reasons that are currently unclear, only about half of all patients respond to the drugs; in the other half, there is almost no change, says Sally Wenzel of National Jewish, who helped conduct several of the preapproval clinical trials.

### Stopping inflammation early

Patients who receive no relief from the leukotriene inhibitors still have reason to hope, however. While the leukotrienes act late in the inflammatory cascade, other ef-

forts are aimed at interrupting it before it gets established. One development propelling that research is the recognition that a particular subset of T lymphocytes seems to be a major culprit in asthma and other allergic diseases, responding with undue vigor to apparently harmless invaders.

In work done nearly a decade ago, researchers working with T cells from mice found they could divide the cells into two groups based on the cytokines they produce. Members of one set, which they called $T_H1$ cells, produce a set of signals that orchestrate attacks on unfamiliar cells, protecting the body against bacteria and tumor cells. Those in the other set—the $T_H2$ cells—produce inflammatory signals normally directed against parasitic invaders. They also encourage the antibody-producing B cells to secrete IgE antibodies, the hallmark of allergies, which help trigger the inflammatory responses.

As researchers learned more about these activity patterns, it became clear that $T_H2$ overactivity is a major factor in asthma. High levels of IgE, for example, are common in asthma patients. And one of the key $T_H2$ cytokines, called interleukin-5 (Il-5 for short), helps trigger the eosinophils that can wreak havoc in asthmatic lungs. Although the distinction between $T_H1$ and $T_H2$ cells is not as cut-and-dried as many might like—many human T cells seem to produce both $T_H1$ and $T_H2$ signals—Yale's Elias says the concept "has opened doors in thinking about asthma" and about potential new therapies.

Some of those efforts are aimed directly at thwarting the effects of $T_H2$ cytokines. For example, Il-5 appears to be a good target. If the cytokine's action in mice is blocked, either by inactivating the gene that codes for the protein or by giving the animal antibodies that prevent Il-5 from binding to and activating eosinophils, the animal's airways do not react to allergens, says immunologist David Huston at Baylor College of Medicine in Houston. This suggests several possible approaches to asthma treatments.

Two pharmaceutical companies, Schering-Plough and SmithKline Beecham, have been working on the development of human versions of mouse anti–Il-5 antibodies, and have been getting promising results in trials with animals—including primates. In the animal trials, the anti–Il-5 antibodies have prevented both eosinophil inflammation and airway constriction. Human trials "are imminent," Huston says.

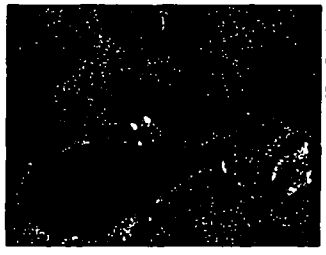
In addition, Huston and his colleagues, as well as a number of industry groups, are working to engineer an inactive version of Il-5 itself that would bind to the cytokine's receptor on eosinophils without triggering the cells, while also preventing the native molecule from binding.

Perhaps closer to pharmacy shelves is an antibody that blocks IgE itself. After $T_H2$ signals trigger B-cell production of an IgE with a particular specificity, the antibody attaches to mast cells, and when it encounters a protein it recognizes as threatening, it triggers the mast cells to unleash their weapons, including leukotrienes and histamine. If there were some way to block the IgE trigger, researchers reasoned, the whole battle could be avoided.

But disarming IgE has proved to be a tricky business. When researchers tried to inactivate it with antibodies, some of their efforts turned out to have just the opposite effect, even triggering fatal allergic reactions. "I've accidentally killed animals with [the wrong kind of] anti-IgE," says Paula Jardieu of Genentech, who has led her company's efforts to develop the therapy. The problem was that these antibodies attached to the same part of IgE that binds the allergen, thus triggering, rather than blocking, IgE's effects on mast cells.

Recently, however, researchers have identified the specific region of IgE that binds to the mast cell receptor, enabling them to produce antibodies that block only that site. Buoyed by promising results in mice, they went on to build a human version of the mouse antibody. Through DNA manipulation, they were able to transplant the IgE-binding region of the mouse molecule onto the base of a human antibody. They tested the resulting "humanized" antibody by giving it to monkeys allergic to ragweed and found that it prevented the typical skin sensitivity to the pollen.

Initial trials, designed to test the safety of this antibody in humans, have been very positive, says Jardieu. The 40 patients who received doses of the antibody suffered only mild reactions when the research team blew allergens into their lungs, with "absolutely no indication of any side effects," Jardieu says. Results from a second round of trials, which tested the antibody's ability to protect 400 asthma patients from natural exposures to allergens, should be published later this summer, says Jardieu, and she expects phase III trials—testing anti-IgE against the best available treatment—to begin this fall.



**Terrible trio.** House dust mite *(top left)*, *Alternaria* mold *(center)*, and birch pollen *(left)* are all common triggers of asthma attacks.

### Tipping the balance against asthma

Another therapeutic strategy currently being investigated aims to short-circuit misplaced $T_H2$ attacks. $T_H1$ and $T_H2$ activities are mutually suppressive: Signals from one cell type inhibit the activity of the other. So several researchers are attempting to take advantage of certain bacteria that induce vigorous $T_H1$ responses, causing the immune system to pump out messengers, such as interleukin-12 and interferon-γ, that inhibit $T_H2$ cell activity.

Some, including Steven Holgate of Southampton University in the United Kingdom, Julian Hopkin of Oxford University, and Graham Rook of University College, London, are working with whole bacteria. They have just begun a series of studies in which they will attempt to protect allergic volunteers from the perils of allergy season by injecting them with a harmless bacterium of the *Mycobacterium* genus, which—like many bacteria—is a strong $T_H1$ inducer. The hope, says Holgate, is that "if we give this to asthmatic subjects, maybe it can switch off the allergies."

Immunologists found a few years ago that it is particular sequences in the bacterial DNA that induce such a strong $T_H1$ response. Those sequences play a key role in a therapy under development by immunologists Eyal Raz and Dennis Carson and allergist David Broide of the University of California, San Diego. The team is attempting to devise a more effective means of desensitizing people to their allergies, which currently involves repeatedly injecting them with small amounts of the allergen, often for years. To bolster this effect, the researchers have designed a small circular piece of DNA, called a plasmid, that includes both the DNA encoding any of several common allergen proteins and fragments of bacterial DNA.

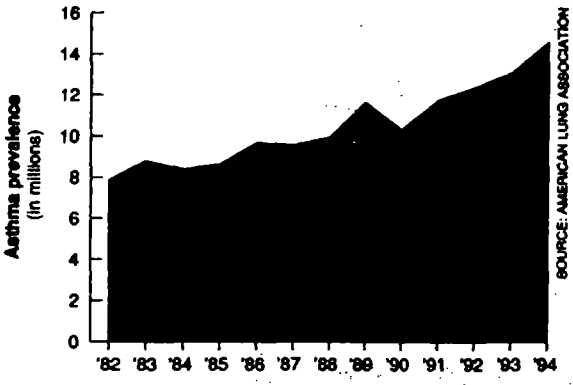
In early tests, the team injected the plasmids into mice, whose skin cells took up the DNA. There the plasmid started producing the antigen protein. "It's like immunotherapy," says Raz, "but instead of having to give it repeatedly, you give it only twice or three times and it is there permanently." At the same time, the researchers hoped, the bacterial DNA in the plasmids would crank up the suppressive effects of the treatment by

# Why the Rise in Asthma Cases?

Asthma is a disease of the industrialized 20th century. First described in the mid-1800s, it may have existed before that time, but was very rare. It is still rare in developing countries. But in the developed world in the last 2 decades, asthma rates have skyrocketed—doubling in the United States since 1980. "Asthma and allergies have become representative of the westernization of our society," says William Busse, an allergist at the University of Wisconsin, Madison.

Researchers do not yet know why. They have come a long way in dissecting the sequence of events that leads to individual asthma attacks: the activation by an allergen or other trigger of certain immune cells, which in turn marshal other cells that mount inflammatory attacks on the lungs (see main text). But why some people are predisposed to such attacks—and why their numbers are now increasing—remain mysteries, although researchers have some clues.

Increased exposure to environmental allergens and immune system changes due to fewer childhood infections may play a role, say some. And geneticists are closing in on a host of genes that have been linked to increased asthma susceptibility. The search for a cause is urgent, says Busse, because it might point to ways of preventing children from developing the disease in the first place. For the moment, he says, "we are treating the consequences of the disease, not preventing it from occurring."




**Asthma ascending.** Researchers are struggling to explain asthma's dramatic increase.

One of the most popular theories holds that asthma has increased partly because of greater exposure to allergens such as house dust mites or cockroaches. Allergist Thomas Platts-Mills of the University of Virginia notes that nowadays children spend more time indoors in front of the television in close contact with carpets and upholstered furniture crawling with dust mites. Still, Platts-Mills says, this "Annette Funicello" effect, as he calls it, "can't explain the rise by itself." The asthma increase is just too great and has occurred even in dry regions where the dust mite is uncommon.

Another feature of modern life might also be contributing: the fall in childhood infections. Early infections, say proponents of this idea, may stimulate a kind of immune response that suppresses later allergic reactions. Earlier this year, Oxford pulmonologist Julian Hopkin and colleagues at the Wakayama Medical Center in Wakayama, Japan, found that children who responded strongly to a skin test indicating that they had been exposed to tuberculosis are less likely to suffer from asthma or other allergic diseases (*Science*, 3 January, p. 77). Similarly, in a study of 1600 Italian soldiers, Paolo Matricardi of the Laboratory of Immunology and Allergy in Rome and his colleagues found that soldiers who tested positive for antibodies to hepatitis A virus—a sign of more childhood infections in general, say the authors—had significantly fewer allergies. (The results appeared in the April *British Medical Journal*.)

Researchers have also turned up other hints that early immunological experience can affect a child's chances of developing asthma—very early experience, if Jill Warner at the University at Southampton in the United Kingdom is right. When she and her colleagues studied immune cells from premature and terminated fetuses, they found that cells from fetuses as young as 22 weeks could multiply when exposed to house dust mites and birch pollen—suggesting that they recognized the allergens from a previous exposure. Warner is currently studying whether limiting a mother's exposure to common allergens can protect her unborn child from later developing allergies and asthma.

Still, environmental influences can't be the full answer, because asthma susceptibility is well known to run in families. A number of all-out hunts are now under way for asthma-susceptibility genes, which might be interacting with environmental factors to drive the rising incidence. So far, only one team—at Sequana Therapeutics Inc. in San Diego—says it has pinpointed a gene, and team members are keeping details of their find under wraps (*Science*, 30 May 1997, p. 1327). But several more public searches are closing in on genes.

A team led by Carol Ober, a geneticist at the University of Chicago, reported at the recent American Thoracic Society meeting that its work with the South Dakota Hutterites, a religious group of 5000 descended from 64 18th-century ancestors, has linked asthma or asthmalike conditions to specific regions on chromosomes 2, 13, and 21. And in a wider study of the general population, the multicenter Collaborative Study on the Genetics of Asthma reported in the April issue of *Nature Genetics* that its researchers have linked asthma in various ethnic groups to a half-dozen different chromosome regions. Other studies have found linkages to regions on chromosomes 11 and 12 containing genes known to code for important players in the inflammation that is part of asthma pathology.

The linkages, like all the other clues, are a long way from solving the asthma riddle, but they are a start. "Everyone knew [the gene search] was a black hole," says Susan Banks-Schlagel, manager of asthma research at the National Heart, Lung, and Blood Institute. "They said, 'Oh, you'll never find anything.' But some interesting things are starting to happen." –G.V.

eliciting production of interferon-γ and other $T_H2$ suppressors.

Again, initial results are promising. Mice receiving the novel immunotherapy have IgE in their blood, fewer eosinophils in their lungs, and less evidence of $T_H2$-type cytokines when they are exposed to the substance to which they were allergic. Raz and his colleagues have formed a company, called Dynavax, and plan to begin human trials in collaboration with researchers at Johns Hopkins University as soon as they receive FDA approval—expected "within the year," says Raz.

But the $T_H2$ model that has inspired these new treatments may not be a complete answer to the asthma puzzle. Viral infections, for example, have been blamed for 80% of severe asthma attacks, says Daniel Rotrosen of the National Institute of Allergy and Infectious Diseases. But viruses have usually

been considered a trigger of a $T_H1$-type response. Some researchers believe that viruses are not the immediate trigger, but contribute to asthma susceptibility by attacking the lining of the lungs, leaving the inner layers more exposed to environmental allergens or other traditional asthma triggers—which would then activate $T_H2$ cells and the other responses they orchestrate. Others believe the viruses may have an inside role, activating certain genes in the nucleus that exacerbate or trigger the inflammatory cascade.

Those unanswered questions might explain why new treatments such as the leukotriene inhibitors will not work for everyone. But the fact that the drugs don't help some patients may be as important as the help they do give some people: "That is where it gets really interesting," Drazen says. "Up until now, we have graded asthma as mild, moderate or severe," which is only of limited help to physicians trying to determine the best course of treatment.

Patients' different responses to the various drugs may help doctors sort out what many suspect is the case: Asthma is not a single disease. Like pneumonia or anemia, Brigham and Women's Drazen says, asthma is a set of symptoms that has varied causes. The new treatments, by getting closer to those causes, may help doctors divide patients into subgroups based on how they respond to treatments, he adds. That, in turn, will help researchers determine how to treat each patient most effectively—a development, certainly, that will help millions breathe easier.

–Gretchen Vogel

IMMUNOLOGY

# New Lead to Safer Marrow Transplants

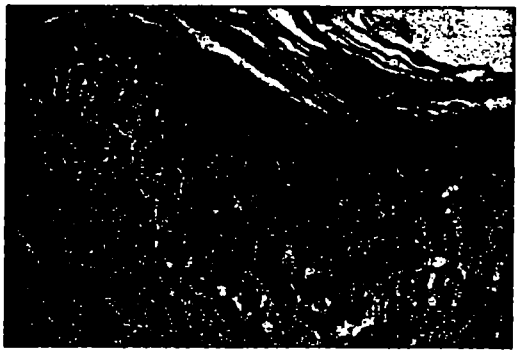
Bone-marrow transplants have become a mainstay of medicine's battle against blood-cell cancers, such as leukemias and lymphomas, as well as against certain noncancerous blood diseases. But in at least half of all patients, the donor immune cells turn against the recipient's own tissues, triggering a deadly ailment called graft-versus-host disease (GVHD). Now a team of doctors led by hematologist Claudio Bordignon at the San Raffaele Scientific Institute in Milan, Italy, may have found a solution to this problem.

On page 1719, the group reports the first successful human test of a gene therapy designed to halt the attack of the donated cells on the recipient's tissues. The researchers genetically engineered the transplanted cells with a self-destruct button that enables doctors to kill them selectively with a drug if they turn mutinous. This allowed the team to wipe out GVHD in two of the three patients who developed it, and partially eliminate it in the third—without using immunosuppressive drugs.

That success is a boost for the struggling field of genetic therapy, says immunologist Drew Pardoll of the Johns Hopkins University School of Medicine in Baltimore, who calls the work "one of a very small cohort of examples in which gene therapy has been shown to have clinical utility." Indeed, if further studies bear out the early promise of the technique, it could make bone-marrow transplants much safer and more effective. Doctors might even start using such transplants more broadly, in patients with less advanced disease. The technique is "very exciting," says immunologist Philip Greenberg of the Fred Hutchinson Cancer Research Center in Seattle. "It has the potential to improve substantially the outcome of [bone-marrow] transplantation."

The strategy's seeds were planted in 1990, when Bordignon first heard about the problems with GVHD [illegible] were cropping up in the top bone-marrow transplant centers, particularly in patients who relapsed and required infusions of donor lymphocytes. Marrow transplants are needed because the high doses of chemotherapeutic drugs and radiation given to leukemia and lymphoma patients in an effort to rid them of all cancer cells also destroy the patients' bone marrow, the vital source of both the red cells and the infection-fighting white cells of the blood.

But unless the donor is an identical twin, the transplant may turn on a patient, causing GVHD, as the foreign white blood cells attack essential organs such as the liver, gut, and skin. Clinicians have sought to avoid this attack by sifting out all of the mature T lymphocytes from the foreign marrow before infusing it. Those are the cells that trigger GVHD, but their removal leaves the patient more vulnerable to infections or cancer relapse. If infection or cancer does develop, the patient can be infused with the donor T cells—again running the risk of GVHD.



Under attack. Multiple lymphocytes are invading the epidermis of human skin with graft-versus-host disease.

GEORGE BALE/FRED HUTCHINSON CANCER [illegible]RCH CENTER

Bordignon, a doctor trained in gene therapy, recalls that he asked himself, "How might one take advantage of gene-transfer technology to control this problem?" He set out in early 1992 to test whether he could introduce a "suicide gene" into these cells, then use the gene to kill the cells if they triggered GVHD. Results with cultured cells looked promising: Lymphocytes engineered with the gene for the enzyme thymidine kinase died when he doused them with the antiviral drug ganciclovir, which the enzyme converts to a deadly poison.

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–Ingrid Wickelgren

# New Clues to Asthma Therapies

**Identification of major players in the inflammatory cascade that damages the lungs in asthma offers targets that may produce better treatments for the disease**

A rising pollen count means itchy eyes, scratchy throats, and stopped-up sinuses for many allergy sufferers, but for those whose allergies trigger asthma, this means more than just discomfort. For them, exposure to usually harmless pollen or other allergens can set off a life-threatening attack in which the airways leading to the lungs close up—making the sufferers feel, they say, as if they are trying to breathe with a full-grown person standing on their chest. These frightening attacks are becoming more and more common. Since 1980, the prevalence of asthma has almost doubled in the United States. Today, it afflicts more than 14 million people in this country alone, and costs almost 5000 lives each year—with no signs of leveling off.

Researchers don't have a clear idea of what is causing this increase (see sidebar). Nor have they worked out what predisposes some people to asthma in the first place. But on one front, they are making real headway. They are beginning to pinpoint many of the key biological players that take part in asthma attacks. And that in turn is providing researchers with openings for new ways to treat asthma, some of which are just entering clinical use. "There is a story that's coming out," says Yale pulmonologist Jack Elias. "It's beginning to hang together."

The main theme of the story is inflammation. Doctors have known for years that asthma attacks are often triggered by allergens, such as cockroaches, dust-mite feces, pollen, or animal hair. Now, researchers are working out the exact cascade of events that these allergens—and other nonallergen triggers such as cold air, viral infections, and exercise—set in motion in the lungs. At the top of the cascade is a particular type of immune cell called the T lymphocyte, which responds to the noxious substances by sending out more than a dozen chemical signals: so-called cytokines, which attract inflammatory cells to the airways of the lungs.

These warriors, in particular those called the eosinophils, release chemical weapons of their own. This second wave of signals, including histamine and small, fatty molecules called leukotrienes, causes blood vessels to leak and lung tissues to swell, contracts the smooth muscles of the airways—cutting off the air supply like squeezing a hose—and encourages mucus production, further clogging already constricted airways. Each crisis causes an immediate difficulty in breathing, and repeated crises over time lead to permanent lung changes that may make the next attack even worse.

Current asthma treatments are aimed at the end result. Bronchodilators open the airways, and antihistamines and steroids reduce inflammation. But by dissecting the chain of command that leads to an attack, researchers have identified a whole new set of promising targets for asthma drugs. "The therapy is moving back closer and closer to the beginning of the inflammation cascade," says Harold Nelson, an allergist and immunologist at the National Jewish Medical and Research Center in Denver. The hope is that these therapies, because of their improved specificity, will be more effective and less liable to cause dangerous side effects than current treatments.

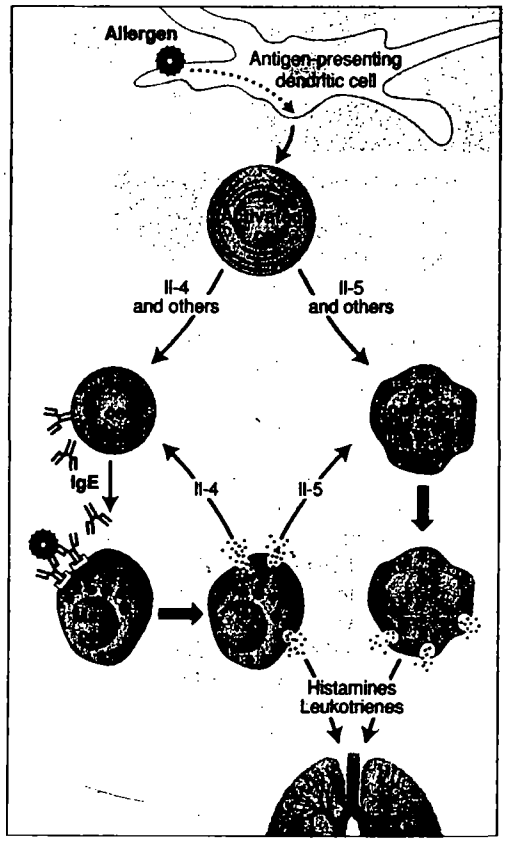



ILLUSTRATION: K. SUTLIFF

**Overzealous warriors.** The T lymphocyte helps command the immune cells—including mast cells and eosinophils—that react to pollen, cold, exercise, and other stimuli to trigger an asthma attack.

Although most of the treatments aimed at the inflammatory cascade are a few years away from patients' medicine cabinets, two have already made it to the shelves. Both drugs, which were approved late last year by the U.S. Food and Drug Administration (FDA), got ahead of the crowd for the simple reason that their targets, the leukotrienes, were implicated in the cascade nearly 50 years ago.

Released by activated eosinophils and other immune-system soldiers recruited to asthmatic lungs, the leukotrienes have several effects that contribute to the airway constriction and inflammation of asthma. They recruit other inflammatory cells, for example. But they are particularly effective in contracting the smooth muscle of the bronchi, the tubes carrying air from the trachea into the lungs. Molecule for molecule, says pulmonologist Jeffrey Drazen of Brigham and Women's Hospital in Boston, the leukotrienes are the most potent bronchoconstrictors ever described—a fact, he adds, "that was not lost on the drug companies," which set out to develop inhibitors.

The two approved last year are Zileuton, which blocks a vital enzyme needed for leukotriene synthesis and is marketed by Abbott Laboratories in Chicago, and Zafirleukast, which blocks the lipid's receptors on smooth muscle and other cells and is produced by Zeneca Pharmaceuticals, based in the United Kingdom. Two more receptor blockers, from Merck and from SmithKline Beecham, are awaiting FDA approval.

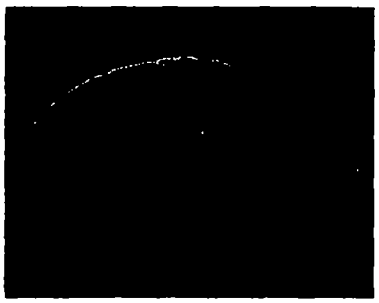
The drugs have worked miracles in some hard-to-treat patients, Drazen says. "In some patients it's like manna from heaven. We treated a veterinarian allergic to dogs and cats who was just miserable. On this treatment, he is a normal person again." But for reasons that are currently unclear, only about half of all patients respond to the drugs; in the other half, there is almost no change, says Sally Wenzel of National Jewish, who helped conduct several of the preapproval clinical trials.

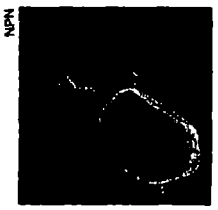
### Stopping inflammation early

Patients who receive no relief from the leukotriene inhibitors still have reason to hope, however. While the leukotrienes act late in the inflammatory cascade, other ef-

forts are aimed at interrupting it before it gets established. One development propelling that research is the recognition that a particular subset of T lymphocytes seems to be a major culprit in asthma and other allergic diseases, responding with undue vigor to apparently harmless invaders.

In work done nearly a decade ago, researchers working with T cells from mice found they could divide the cells into two groups based on the cytokines they produce. Members of one set, which they called $T_H1$ cells, produce a set of signals that orchestrate attacks on unfamiliar cells, protecting the body against bacteria and tumor cells. Those in the other set—the $T_H2$ cells—produce inflammatory signals normally directed against parasitic invaders. They also encourage the antibody-producing B cells to secrete IgE antibodies, the hallmark of allergies, which help trigger the inflammatory responses.




As researchers learned more about these activity patterns, it became clear that $T_H2$ overactivity is a major factor in asthma. High levels of IgE, for example, are common in asthma patients. And one of the key $T_H2$ cytokines, called interleukin-5 (Il-5 for short), helps trigger the eosinophils that can wreak havoc in asthmatic lungs. Although the distinction between $T_H1$ and $T_H2$ cells is not as cut-and-dried as many might like—many human T cells seem to produce both $T_H1$ and $T_H2$ signals—Yale's Elias says the concept "has opened doors in thinking about asthma" and about potential new therapies.

Some of those efforts are aimed directly at thwarting the effects of $T_H2$ cytokines. For example, Il-5 appears to be a good target. If the cytokine's action in mice is blocked, either by inactivating the gene that codes for the protein or by giving the animal antibodies that prevent Il-5 from binding to and activating eosinophils, the animal's airways do not react to allergens, says immunologist David Huston at Baylor College of Medicine in Houston. This suggests several possible approaches to asthma treatments.

Two pharmaceutical companies, Schering-Plough and SmithKline Beecham, have been working on the development of human versions of mouse anti–Il-5 antibodies, and have been getting promising results in trials with animals—including primates. In the animal trials, the anti–Il-5 antibodies have prevented both eosinophil inflammation and airway constriction. Human trials "are imminent," Huston says.

In addition, Huston and his colleagues, as well as a number of industry groups, are working to engineer an inactive version of Il-5 itself that would bind to the cytokine's receptor on eosinophils without triggering the cells, while also preventing the native molecule from binding.

Perhaps closer to pharmacy shelves is an antibody that blocks IgE itself. After $T_H2$ signals trigger B-cell production of an IgE with a particular specificity, the antibody attaches to mast cells, and when it encounters a protein it recognizes as threatening, it triggers the mast cells to unleash their weapons, including leukotrienes and histamine. If there were some way to block the IgE trigger, researchers reasoned, the whole battle could be avoided.

But disarming IgE has proved to be a tricky business. When researchers tried to inactivate it with antibodies, some of their efforts turned out to have just the opposite effect, even triggering fatal allergic reactions. "I've accidentally killed animals with [the wrong kind of] anti-IgE," says Paula Jardieu of Genentech, who has led her company's efforts to develop the therapy. The problem was that these antibodies attached to the same part of IgE that binds the allergen, thus triggering, rather than blocking, IgE's effects on mast cells.


**Terrible trio.** House dust mite *(top left)*, *Alternaria* mold *(center)*, and birch pollen *(left)* are all common triggers of asthma attacks.

Recently, however, researchers have identified the specific region of IgE that binds to the mast cell receptor, enabling them to produce antibodies that block only that site. Buoyed by promising results in mice, they went on to build a human version of the mouse antibody. Through DNA manipulation, they were able to transplant the IgE-binding region of the mouse molecule onto the base of a human antibody. They tested the resulting "humanized" antibody by giving it to monkeys allergic to ragweed and found that it prevented the typical skin sensitivity to the pollen.

Initial trials, designed to test the safety of this antibody in humans, have been very positive, says Jardieu. The 40 patients who received doses of the antibody suffered only mild reactions when the research team blew allergens into their lungs, with "absolutely no indication of any side effects," Jardieu says. Results from a second round of trials, which tested the antibody's ability to protect 400 asthma patients from natural exposures to allergens, should be published later this summer, says Jardieu, and she expects phase III trials—testing anti-IgE against the best available treatment—to begin this fall.

### Tipping the balance against asthma

Another therapeutic strategy currently being investigated aims to short-circuit misplaced $T_H2$ attacks. $T_H1$ and $T_H2$ activities are mutually suppressive: Signals from one cell type inhibit the activity of the other. So several researchers are attempting to take advantage of certain bacteria that induce vigorous $T_H1$ responses, causing the immune system to pump out messengers, such as interleukin-12 and interferon-γ, that inhibit $T_H2$ cell activity.

Some, including Steven Holgate of Southampton University in the United Kingdom, Julian Hopkin of Oxford University, and Graham Rook of University College, London, are working with whole bacteria. They have just begun a series of studies in which they will attempt to protect allergic volunteers from the perils of allergy season by injecting them with a harmless bacterium of the *Mycobacterium* genus, which—like many bacteria—is a strong $T_H1$ inducer. The hope, says Holgate, is that "if we give this to asthmatic subjects, maybe it can switch off the allergies."

Immunologists found a few years ago that it is particular sequences in the bacterial DNA that induce such a strong $T_H1$ response. Those sequences play a key role in a therapy under development by immunologists Eyal Raz and Dennis Carson and allergist David Broide of the University of California, San Diego. The team is attempting to devise a more effective means of desensitizing people to their allergies, which currently involves repeatedly injecting them with small amounts of the allergen, often for years. To bolster this effect, the researchers have designed a small circular piece of DNA, called a plasmid, that includes both the DNA encoding any of several common allergen proteins and fragments of bacterial DNA.

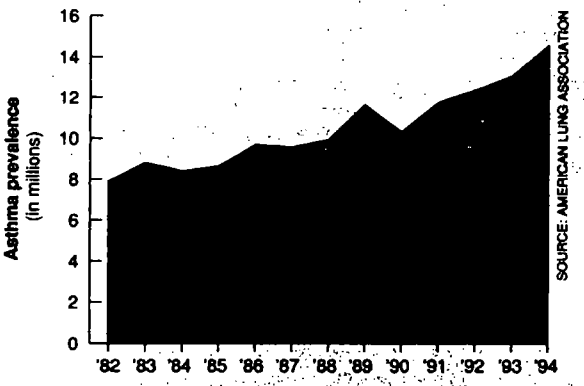
In early tests, the team injected the plasmids into mice, whose skin cells took up the DNA. There the plasmid started producing the antigen protein. "It's like immunotherapy," says Raz, "but instead of having to give it repeatedly, you give it only twice or three times and it is there permanently." At the same time, the researchers hoped, the bacterial DNA in the plasmids would crank up the suppressive effects of the treatment by

# Why the Rise in Asthma Cases?

Asthma is a disease of the industrialized 20th century. First described in the mid-1800s, it may have existed before that time, but was very rare. It is still rare in developing countries. But in the developed world in the last 2 decades, asthma rates have skyrocketed—doubling in the United States since 1980. "Asthma and allergies have become representative of the westernization of our society," says William Busse, an allergist at the University of Wisconsin, Madison.

Researchers do not yet know why. They have come a long way in dissecting the sequence of events that leads to individual asthma attacks: the activation by an allergen or other trigger of certain immune cells, which in turn marshal other cells that mount inflammatory attacks on the lungs (see main text). But why some people are predisposed to such attacks—and why their numbers are now increasing—remain mysteries, although researchers have some clues.

Increased exposure to environmental allergens and immune system changes due to fewer childhood infections may play a role, say some. And geneticists are closing in on a host of genes that have been linked to increased asthma susceptibility. The search for a cause is urgent, says Busse, because it might point to ways of preventing children from developing the disease in the first place. For the moment, he says, "we are treating the consequences of the disease, not preventing it from occurring."




**Asthma ascending.** Researchers are struggling to explain asthma's dramatic increase.

One of the most popular theories holds that asthma has increased partly because of greater exposure to allergens such as house dust mites or cockroaches. Allergist Thomas Platts-Mills of the University of Virginia notes that nowadays children spend more time indoors in front of the television in close contact with carpets and upholstered furniture crawling with dust mites. Still, Platts-Mills says, this "Annette Funicello" effect, as he calls it, "can't explain the rise by itself." The asthma increase is just too great and has occurred even in dry regions where the dust mite is uncommon.

Another feature of modern life might also be contributing: the fall in childhood infections. Early infections, say proponents of this idea, may stimulate a kind of immune response that suppresses later allergic reactions. Earlier this year, Oxford pulmonologist Julian Hopkin and colleagues at the Wakayama Medical Center in Wakayama, Japan, found that children who responded strongly to a skin test indicating that they had been exposed to tuberculosis are less likely to suffer from asthma or other allergic diseases (*Science*, 3 January, p. 77). Similarly, in a study of 1600 Italian soldiers, Paolo Matricardi of the Laboratory of Immunology and Allergy in Rome and his colleagues found that soldiers who tested positive for antibodies to hepatitis A virus—a sign of more childhood infections in general, say the authors—had significantly fewer allergies. (The results appeared in the April *British Medical Journal*.)

Researchers have also turned up other hints that early immunological experience can affect a child's chances of developing asthma—very early experience, if Jill Warner at the University at Southampton in the United Kingdom is right. When she and her colleagues studied immune cells from premature and terminated fetuses, they found that cells from fetuses as young as 22 weeks could multiply when exposed to house dust mites and birch pollen—suggesting that they recognized the allergens from a previous exposure. Warner is currently studying whether limiting a mother's exposure to common allergens can protect her unborn child from later developing allergies and asthma.

Still, environmental influences can't be the full answer, because asthma susceptibility is well known to run in families. A number of all-out hunts are now under way for asthma-susceptibility genes, which might be interacting with environmental factors to drive the rising incidence. So far, only one team—at Sequana Therapeutics Inc. in San Diego—says it has pinpointed a gene, and team members are keeping details of their find under wraps (*Science*, 30 May 1997, p. 1327). But several more public searches are closing in on genes.

A team led by Carol Ober, a geneticist at the University of Chicago, reported at the recent American Thoracic Society meeting that its work with the South Dakota Hutterites, a religious group of 5000 descended from 64 18th-century ancestors, has linked asthma or asthmalike conditions to specific regions on chromosomes 2, 13, and 21. And in a wider study of the general population, the multicenter Collaborative Study on the Genetics of Asthma reported in the April issue of *Nature Genetics* that its researchers have linked asthma in various ethnic groups to a half-dozen different chromosome regions. Other studies have found linkages to regions on chromosomes 11 and 12 containing genes known to code for important players in the inflammation that is part of asthma pathology.

The linkages, like all the other clues, are a long way from solving the asthma riddle, but they are a start. "Everyone knew [the gene search] was a black hole," says Susan Banks-Schlagel, manager of asthma research at the National Heart, Lung, and Blood Institute. "They said, 'Oh, you'll never find anything.' But some interesting things are starting to happen." –G.V.

eliciting production of interferon-γ and other $T_H2$ suppressors.

Again, initial results are promising. Mice receiving the novel immunotherapy have less IgE in their blood, fewer eosinophils in their lungs, and less evidence of $T_H2$-type cytokines when they are exposed to the substance to which they were allergic. Raz and his colleagues have formed a company, called Dynavax, and plan to begin human trials in collaboration with researchers at Johns Hopkins University as soon as they receive FDA approval—expected "within the year," says Raz.

But the $T_H2$ model that has inspired these new treatments may not be a complete answer to the asthma puzzle. Viral infections, for example, have been blamed for 80% of severe asthma attacks, says Daniel Rotrosen of the National Institute of Allergy and Infectious Diseases. But viruses have usually

been considered a trigger of a $T_H1$-type response. Some researchers believe that viruses are not the immediate trigger, but contribute to asthma susceptibility by attacking the lining of the lungs, leaving the inner layers more exposed to environmental allergens or other traditional asthma triggers—which would then activate $T_H2$ cells and the other responses they orchestrate. Others believe the viruses may have an inside role, activating certain genes in the nucleus that exacerbate or trigger the inflammatory cascade.

Those unanswered questions might explain why new treatments such as the leukotriene inhibitors will not work for everyone. But the fact that the drugs don't help some patients may be as important as the help they do give some people: "That is where it gets really interesting," Drazen says. "Up until now, we have graded asthma as mild, moderate or severe," which is only of limited help to physicians trying to determine the best course of treatment.

Patients' different responses to the various drugs may help doctors sort out what many suspect is the case: Asthma is not a single disease. Like pneumonia or anemia, Brigham and Women's Drazen says, asthma is a set of symptoms that has varied causes. The new treatments, by getting closer to those causes, may help doctors divide patients into subgroups based on how they respond to treatments, he adds. That, in turn, will help researchers determine how to treat each patient most effectively—a development, certainly, that will help millions breathe easier.

–Gretchen Vogel

IMMUNOLOGY

# New Lead to Safer Marrow Transplants

Bone-marrow transplants have become a mainstay of medicine's battle against blood-cell cancers, such as leukemias and lymphomas, as well as against certain noncancerous blood diseases. But in at least half of all patients, the donor immune cells turn against the recipient's own tissues, triggering a deadly ailment called graft-versus-host disease (GVHD). Now a team of doctors led by hematologist Claudio Bordignon at the San Raffaele Scientific Institute in Milan, Italy, may have found a solution to this problem.

On page 1719, the group reports the first successful human test of a gene therapy designed to halt the attack of the donated cells on the recipient's tissues. The researchers genetically engineered the transplanted cells with a self-destruct button that enables doctors to kill them selectively with a drug if they turn mutinous. This allowed the team to wipe out GVHD in two of the three patients who developed it, and partially eliminate it in the third—without using immunosuppressive drugs.

That success is a boost for the struggling field of genetic therapy, says immunologist Drew Pardoll of the Johns Hopkins University School of Medicine in Baltimore, who calls the work "one of a very small cohort of examples in which gene therapy has been shown to have clinical utility." Indeed, if further studies bear out the early promise of the technique, it could make bone-marrow transplants much safer and more effective. Doctors might even start using such transplants more broadly, in patients with less advanced disease. The technique is "very exciting," says immunologist Philip Greenberg of the Fred Hutchinson Cancer Research Center in Seattle. "It has the potential to improve substantially the outcome of [bone-marrow] transplantation."

The strategy's seeds were planted in 1990, when Bordignon first heard about the problems with GVHD that were cropping up in the top bone-marrow transplant centers, particularly in patients who relapsed and required infusions of donor lymphocytes. Marrow transplants are needed because the high doses of chemotherapeutic drugs and radiation given to leukemia and lymphoma patients in an effort to rid them of all cancer cells also destroy the patients' bone marrow, the vital source of both the red cells and the infection-fighting white cells of the blood.

But unless the donor is an identical twin, the transplant may turn on a patient, causing GVHD, as the foreign white blood cells attack essential organs such as the liver, gut, and skin. Clinicians have sought to avoid this attack by sifting out all of the mature T lymphocytes from the foreign marrow before infusing it. Those are the cells that trigger GVHD, but their removal leaves the patient more vulnerable to infections or cancer relapse. If infection or cancer does develop, the patient can be infused with the donor T cells—again running the risk of GVHD.

**Under attack.** Multiple lymphocytes are invading the epidermis of human skin with graft-versus-host disease.

GEORGE SALE/FRED HUTCHINSON CANCER RESEARCH CENTER

Bordignon, a doctor trained in gene therapy, recalls that he asked himself, "How might one take advantage of gene-transfer technology to control this problem?" He set out in early 1992 to test whether he could introduce a "suicide gene" into these cells, then use the gene to kill the cells if they triggered GVHD. Results with cultured cells looked promising: Lymphocytes engineered with the gene for the enzyme thymidine kinase died when he doused them with the antiviral drug ganciclovir, which the enzyme converts to a deadly poison.

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–Ingrid Wickelgren

ing the November 1995 assault on Jaffna. Cease-fires have been declared in Sudan for both polio and dracunculiasis eradication, expanding health truces beyond immunization.

Days of tranquillity permit warring parties to disengage and provide a glimpse of peace, but also give both sides a common goal to serve as a starting point for future negotiations. The resolution of conflict with incorporation of the rebels into the national army in El Salvador and, recently, in the Philippines provides evidence that days of tranquillity can be the first of many steps toward a lasting peace. Polio eradication activities must be conducted amidst current and future conflicts around the world. We are confident that there will be more truces and polio will be eradicated. The challenge for science is to continue the development of tasks and tools that can serve as instruments of peace.

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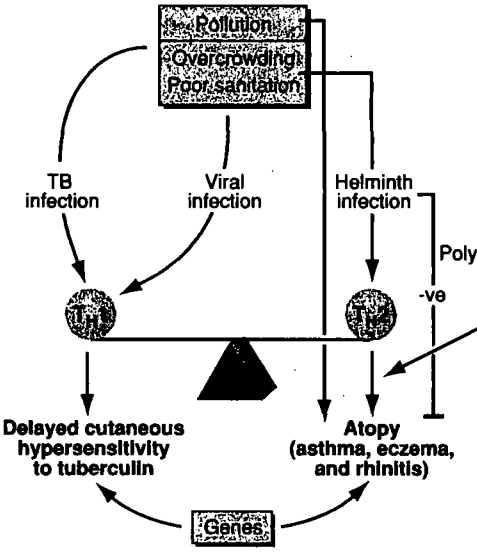
IMMUNOLOGY

# Asthma: An Epidemic in the Absence of Infection?

William O. C. M. Cookson and Miriam F. Moffatt

Asthma is a chronic and debilitating disease, causing swollen and inflamed airways that are prone to constrict suddenly and violently. Asthmatics have attacks of shortness of breath and wheezing that can be life-threatening or even fatal. The prevalence of asthma in Westernized societies has risen steadily this century, doubling in the last 20 years (*1*). Asthma now affects one child in seven in Great Britain, and in the United States it causes one-third of pediatric emergency-room visits. Asthma is familial, and genome-wide searches by our group and others have shown that many genetic loci predispose to the disease (*2*). It is unlikely, however, that the genetic makeup of stable populations can change significantly within one century, so the probable cause of the epidemic must lie in the environment. In this issue of *Science*, Shirakawa and his colleagues (p. 77) present evidence for a novel environmental cause of asthma (*3*).

Asthmatic airway inflammation is initiated by immunoglobulin E (IgE)–mediated allergy ("atopy") to airborne proteins ("allergens"). For asthmatics, the most important source of allergens is the house dust mite. These mites thrive in warm, moist conditions and are ubiquitous in human bedding. There is a dose-response relation between exposure to mite antigens and asthma, and a plausible but unproven case can be made for increasing levels of mite in modern heated homes (*1*). In Japan, asthma has increased just as the population has moved away from the traditional bare and well-ventilated house to Western-style buildings. In Arizona, however, the dry heat means that mite allergy is rare, yet asthma is as common in Tucson as elsewhere in the United States. This suggests that the innate ability to become allergic can readily find alternative antigens.




**An advantage of infection.** Atopy (asthma and other allergic diseases) is reciprocally related to immunity to tuberculosis (as measured by delayed cutaneous hypersensitivity to tuberculin) (*3*). If an individual has predominantly $T_H2$ T cells, the $T_H2$ phenotype interacts with environmental allergens to produce atopic disease. Infections may alter the balance between $T_H1$ and $T_H2$ phenotypes. The clean living conditions of Western society, by reducing the incidence of infection, may tip the balance toward the $T_H2$ phenotype and predispose to asthma.

Air pollution may aggravate existing asthma but is not responsible for the asthma epidemic (*1*). Comparisons have been made between the prevalence of asthma and allergy in highly polluted Leipzig in East Germany and clean Munich in the West (*4*). Surprisingly, the prevalence of asthma and skin tests to common allergens was lower in the East. Similar comparisons between Sweden and polluted Poland show the same phenomenon (*5*). The German investigators also found that the prevalence of asthma was lower in the youngest children of large families than in children high in the birth order (*6*).

These results suggest that asthma prevalence has increased because of something lacking in the modern environment, rather than through the positive actions of some toxic factor. Respiratory and other infections are much more common in polluted and crowded Eastern block countries than in the West, and younger children get more infections from their siblings than single or older children. Childhood infections may, therefore, paradoxically protect against asthma. The study by Shirakawa *et al.* on children in Japan focuses on tuberculosis as a key infection influencing asthma prevalence (*3*).

Inflammation is modulated by helper T ($T_H$) lymphocytes. T lymphocytes may be classified into $T_H1$ and $T_H2$ types, according to the pattern of their cytokine production (*7*). $T_H1$ cells secrete interferon-γ (IFN-γ), interleukin-2 (IL-2), and lymphotoxin, whereas $T_H2$ cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13. $T_H1$ cells enhance cellular immune responses, and $T_H2$ cells favor the humoral response. Although the $T_H1/T_H2$ classification is an oversimplification, cells exhibiting the $T_H2$ phenotype upregulate IgE production and are prominent in the pathogenesis of airway inflammation and asthma.

As in other modern societies, infection with *Mycobacterium tuberculosis* (Mtb) has declined steadily in Japan during this century. This is in part due to a comprehensive program of inoculation with attenuated bovine tuberculosis vaccine bacillus Calmette-Guérin (BCG), which is administered at 3 months of age. Children are tested for delayed hypersensitivity to tuberculin (DHT) at 6 and 7 years of age and are re-inoculated with BCG if the skin test is negative. Final skin testing is carried out on all children when they are 12. Shirakawa *et al.* studied 867 children after the age of 12 and showed a clear negative relation between DHT responses and two parameters—the presence of asthma and the serum IgE concentration.

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Children with positive DHT responses to tuberculin had serum cytokine concentrations suggestive of predominant $T_H1$ responses, in contrast to the $T_H2$ profiles seen in children with negative DHTs.

These results are an important extension of observations in the 1960s and 1970s that there is a reciprocal relation between inflammatory and humoral responses to vaccination regimes (*7*, *8*). This reciprocal relation has also been attributed to preferential activation of $T_H1$ or $T_H2$ subsets of T cells and is consistent with the genetic predisposition to $T_H1$ or $T_H2$ responses of different strains of mice.

Central to the relevance of the results is the hypothesis that the immune system can be manipulated to manifest a persistent $T_H1$ or $T_H2$ response. If this is the case, vaccination to induce $T_H1$ responses may be effective against asthma and other allergic disorders (9). In mice, overwhelming *Schistosoma mansoni* infection induces $T_H2$ responses. The infection concomitantly down-regulates the $T_H1$ response to other antigens and delays the clearance of vaccinia virus (*10*). However, in humans with filariasis, who show $T_H2$-biased cytokine profiles, the ability to respond to Mtb proteins is not lost (*11*). Children with eczema, another atopic condition, occasionally undergo spontaneous remission after severe bacterial or viral infections (*12*), although usually temporarily. Both of these observations suggest that alterations in the $T_H2/T_H1$ balance may become important only in the presence of continued overwhelming infection.

Also confusing the $T_H1/T_H2$ theory of asthma are the findings that helminth and other parasite infection may protect against allergic diseases, despite up-regulation of $T_H2$ responses. This type of infestation is invoked to explain the low prevalence of asthma in rural Africa and the Venezuelan slums (*13*, *14*). Helminth infection produces high levels of polyclonal IgE that, possibly by saturating the number of binding sites for IgE on mast and other effector cells of allergy, prevent activation of these cells by the relatively trivial exposures to allergens.

Thus, the results of Shirakawa *et al.* invite the speculation that the decline in childhood tuberculosis infection in Japan is causal in the recent asthma epidemic. However, the incidence of other infections may also be declining, so the case for tuberculosis requires further study. Nevertheless, the new results emphasize the complexity of the environmental contribution to asthma and remind us that identification of the relevant factors may ultimately resolve this epidemic.

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SIGNAL TRANSDUCTION

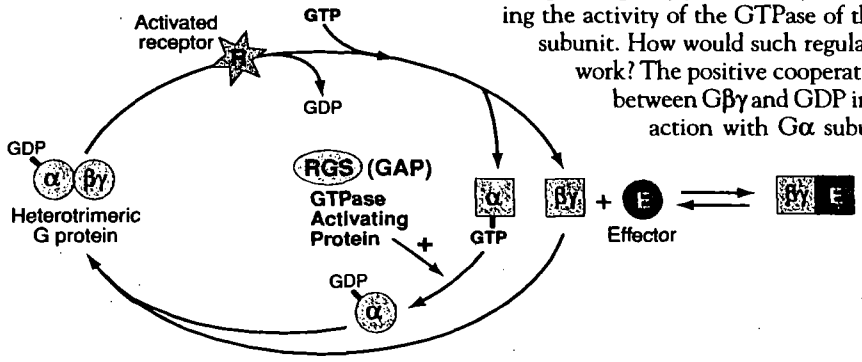
# There Are GAPS and There Are GAPS


Ravi Iyengar


Although their main function is to regulate other proteins, guanine nucleotide–binding proteins (G proteins) are also guanosine triphosphatases (GTPases), cleaving guanosine triphosphate (GTP) to form guanosine diphosphate (GDP). Because of this activity, they oscillate between GTP- and GDP-bound states, and thus regulate diverse processes such as protein synthesis, cytoskeleton assembly, vesicle transport, and signal transduction. The superfamily comprises both small monomeric and large multimeric G proteins, but for all members, the release of bound GDP and the binding of GTP are highly regulated processes (*1*). The GTPase activity of small G proteins, such as EF-Tu and Ras, is stimulated by associated proteins called GAPs (GTPase activating proteins) (*2*). But GAPs for most large G proteins had not been described until recent work identified members of the regulators of G protein–signaling (RGS) family as GAPs for this subfamily.

The large heterotrimeric G proteins involved in signal transduction have α subunits, which are related to small G proteins, and βγ subunits that exist as a single complex. Both Gα and Gβγ can independently transmit signals (*3*). Signal termination for both Gα and Gβγ subunits likely occurs through GTP hydrolysis. How the GTPase terminates signaling through Gα subunits is easily understood given the observation that GDP-Gα subunits have much lower affinities for effectors than do GTP-Gα complexes (*4*). But how signaling through Gβγ is terminated has not been as clear. A report in *Cell* by Gilman and co-workers (5) and two others in *Nature* (6) identifying two members of the RGS family, GAIP and RGS4, as GAPs for members of the $G\alpha_i$ family and other recent papers shed light on this issue.

Members of the RGS family have been identified in yeast, *Caenorhabditis elegans*, and mammals (*7*). Sst2p in yeast and EGL-10 in *C. elegans*, homologs of RGS, suppress signal transmission by acting on the G protein–α subunit (*8*). Mammalian RGS can substitute for yeast Sst2p in regulating pheromone signaling (9), which is transmitted through Gβγ subunits (*10*). Taken together, these data suggest that RGS can regulate signaling through Gβγ subunits by modulating the activity of the GTPase of the α subunit. How would such regulation work? The positive cooperativity between Gβγ and GDP interaction with Gα subunits




**A four-component heterotrimeric G protein–signaling system.** The resting G protein is an αβγ heterotrimer with GDP bound to it. Activated receptor promotes the release of GDP, the binding of GTP, and dissociation of GTP-Gα from the Gβγ complex. GTP-Gα and Gβγ can now interact with their effectors and propagate the signal. RGS stimulates (+) the GTPase activity of the Gα subunit, resulting in the accumulation of GDP-Gα, which re-forms the stable heterotrimer. Free Gβγ leads to dissociation of Gβγ from effector, thus terminating signal propagation. R, receptor; E, effector; αβγ, the heterotrimeric G protein; and RGS (GAP), stimulator of the GTPase of the Gα subunit.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11. A primary peptide library, KNXXXXXXXX-COOH, where X indicates all amino acids except Cys and Trp, was first used to screen peptides that bind specifically to the glutathione-S-transferase (GST)–PDZ domains. All the peptides in the library end with free carboxylate, therefore orienting all binding pockets. The peptides that bound were sequenced as a mixture, and the selectivities for amino acids at a given position were determined by comparison to the sequence of control experiments with GST alone (*10*). Arg was not included in the calculation because of buffer contamination during sequencing. A secondary library, KNXXXXXX(S,T,Y)XX-COOH, where the −2 position was fixed with Ser, Thr, and Tyr, was used to further define the preference of some PDZ domains.
12. Peptide library synthesis was as described (*10*). Individual PDZ domains were expressed and purified as GST fusion proteins: murine hDlg PDZ-1 (186–282), PDZ-2 (281–377), PDZ-3 (428–518), and PDZ-1/2 (281–518); murine PTPbas PDZ-3 (1351–1445) and PDZ-5 (1758–1848); murine Tiam-1 PDZ; human LIN-2 PDZ (422–507); human erythroid p55 PDZ (1–164); and human AF-6 PDZ (983–1102). Glutathione beads (50 to 60 μl) saturated with GST-PDZ proteins were mixed with the peptide library (1 mg) in 300 μl of TSN buffer [40 mM triethylamine (pH 7.6), 150 mM NaCl, and 0.01% NP-40] containing bovine serum albumin (BSA, 1 mg/ml) and 1 mM dithiothreitol (DTT). After 45 min of constant shaking at 4°C, the beads were washed with TSN buffer. The peptides retained were eluted with 30% acetic acid, lyophilized, resuspended in distilled water, and sequenced on a Bio-Applied 477A sequencer.
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# The Inverse Association Between Tuberculin Responses and Atopic Disorder

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Human immune responses are heterogeneous and may involve antagonism between T helper ($T_H$) lymphocyte subsets and their cytokines. Atopy is characterized by immediate immunoglobulin E (IgE)–mediated hypersensitivity to agents such as dust mites and pollen, and it underlies the increasingly prevalent disorder asthma. Among Japanese schoolchildren, there was a strong inverse association between delayed hypersensitivity to *Mycobacterium tuberculosis* and atopy. Positive tuberculin responses predicted a lower incidence of asthma, lower serum IgE levels, and cytokine profiles biased toward $T_H1$ type. Exposure and response to *M. tuberculosis* may, by modification of immune profiles, inhibit atopic disorder.

Atopy is a state of allergic response, mediated by IgE, to largely innocuous, common environmental antigens (allergens) such as those derived from house dust mites and plant pollens (*1*); it underlies the clinical diseases of asthma, hay fever, and eczema (*2*). Atopy can be recognized by allergen-specific IgE in serum or by immediate-type hypersensitivity reactions to allergens upon intradermal skin testing. Heterogeneous genetic and environmental factors interact in the development of atopy (*3*); a set of cytokines—interleukin-4 (IL-4), IL-10, and IL-13 derived from the $T_H2$ subset of T lymphocytes—is central in mediating IgE production and the development of immediate hypersensitivity (*4*).

In recent decades there has been an increase in severity, and probably in prevalence, of atopic disorders in developed countries (*5*). Studies on migrants from developing to developed countries support the importance of etiological environmental changes associated with "Westernization" (*6*). The nature of these environmental changes is obscure, but speculation has focused on increased air pollution or other toxins in the environment, increased indoor exposure to dust mite antigens in less ventilated modern homes, and dietary changes (*7*). One factor temporally associated with the rise of atopy is the decline of many infectious diseases in developed countries as the result of improved living standards and immunization programs (*8*). Data on the risk of atopy according to sibship size and birth order (*9*) also support the possibility that diminished exposure to infection might, in some way, promote atopic responses. Childhood respiratory infections that might strongly modify the developing immune system, both systemically and within the lung, include measles, whooping cough, and tuberculosis. Some of these infections cultivate a $T_H1$ immunological environment with IL-12, interferon-γ (IFN-γ), and tumor necrosis factor (TNF) as predominant cytokines (*10*); because these cytokines inhibit $T_H2$ cytokine functions (*11*), the absence of such infections might release $T_H2$ immune mechanisms and thus promote atopic disorder.

In the case of tuberculosis, an important marker of $T_H1$-mediated acquired immunity (not synonymous with protection) is the development of delayed-type hypersensitivity. This can be tested by observing the reaction, after 48 hours, to the intradermal injection of tuberculin protein (*12*). There is likely a "J-shaped" relation between the degree of delayed hypersensitivity and the risk of tuberculous disease, in which people with moderate hypersensitivity are at least risk (*13*).

To test for clinical evidence of antagonism between delayed hypersensitivity to tuberculin and immediate atopic responses, we conducted an epidemiologic survey in a county of the Wakayama prefecture in southern Honshu, Japan, where there has been a long-established program of tuberculin testing and immunization with attenuated bovine *M. tuberculosis* vaccine [bacillus Calmette-Guérin (BCG)] after birth and at 6 and 12 years of age (*14*). From a population of approximately 1000 12- to 13-year-old schoolchildren attending the 18 junior high schools of the county in 1995, we studied 867 children with complete retrospective records of their tuberculin responses. We administered a

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questionnaire documenting atopic symptoms and social and environmental variables, and we also measured IgE serum levels and $T_H1$ and $T_H2$ cytokine profiles (*15*); these data were analyzed in relation to the record of tuberculin responses.

There was a bimodal distribution of delayed-type hypersensitivity responses to tuberculin upon skin testing (Fig. 1A). Positive tuberculin tests (≥10 mm skin induration) correspond to response to *M. tuberculosis*; negative tests include fully negative reactions as well as intermediate reactions (5 to 9 mm) that generally reflect responses to nontuberculous environmental mycobacteria or to BCG (*16*). Positive tuberculin responses were recorded in 3% of the children at 3 months of age, in 33.2% at 6 years, and in 58.0% at 12 years. In many children, the tuberculin status changed, to either positive or negative, between the ages of 6 and 12 years (Table 1, groups 2 and 4). None of the children suffered clinical tuberculous disease at any stage, including 24 with florid tuberculin responses (>40 mm skin induration) who underwent full clinical and radiographic assessment for the disease.

Of all the children studied, 36% manifested atopic symptoms at some time. A strong inverse association was found between positive tuberculin responses at both 6 and 12 years of age and a range of atopic characteristics, including symptoms at any age and IgE levels and $T_H2$ cytokine profiles assayed at 12 years of age (Fig. 1B and Tables 1 and 2). In positive tuberculin responders, the rate of current atopic symptoms was one-third the rate in negative responders. Asthmatic symptoms were one-half to one-third as likely in positive tuberculin responders as in negative responders (Table 2). Moreover, remission of atopic symptoms between 7 and 12 years of age was six to nine times as likely in positive tuberculin responders. Serum IgE levels, both total and allergen-specific, were also lower in the positive tuberculin responders. The geometric mean for total serum IgE level was 112

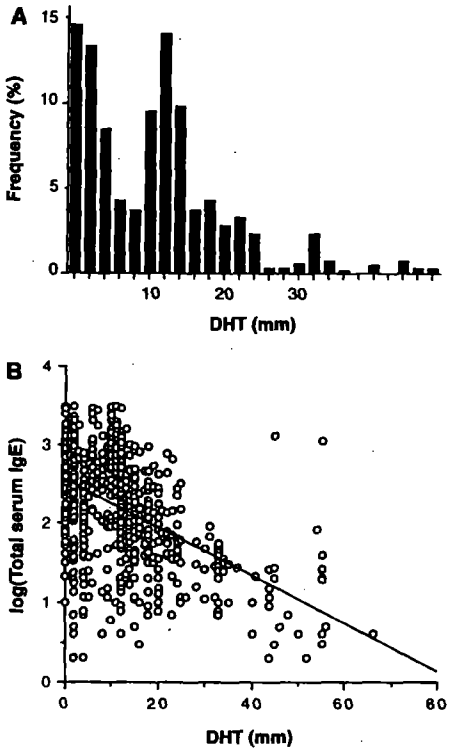


**Fig. 1.** Delayed hypersensitivity to tuberculin (DHT, in millimeters) and relation to serum IgE. **(A)** Histogram showing bimodal distribution of responses to tuberculin, assayed as DHT at 12 years of age in 867 Japanese schoolchildren. **(B)** Plot of log(total serum IgE) versus DHT in the same children ($r = -0.492$, $P < 0.001$).

**Table 1.** History of infectious diseases, atopic symptoms, IgE levels, and cytokine profiles in subjects grouped by tuberculin reactivity. ASE, allergen-specific IgE; UD, undetectable.

| Measurement | Group 1 ($n$ = 290) | Group 2 ($n$ = 289) | Group 3 ($n$ = 213) | Group 4 ($n$ = 75) | Total ($n$ = 867) |
|---|---|---|---|---|---|
| Tuberculin response | | | | | |
| At 6 years | − | − | + | + | |
| At 12 years | − | + | + | − | |
| Positive antiviral immunity (%) | | | | | |
| Measles (history + vaccine) | 83.4 | 87.2 | 84.5 | 81.3 | 84.3 |
| Chicken pox (history + vaccine) | 86.9 | 82.3 | 82.2 | 82.7 | 83.9 |
| Mumps (history + vaccine) | 62.8 | 60.9 | 60.1 | 57.3 | 61.0 |
| Number with IgE to *Ascaris* | 2 | 2 | 2 | 1 | 7 |
| Symptoms (%) | | | | | |
| Atopy (past + present) | 46.8 | 33.9‡‡ | 25.8‡‡ | 38.7 | 36.6 |
| Atopy (present) | 32.1 | 7.9‡‡‡ | 9.8‡‡‡ | 30.7 | 18.5 |
| Asthma (past + present) | 13.4 | 4.1‡‡ | 3.7‡‡ | 6.8 | 7.4 |
| Rhinitis (past + present) | 16.2 | 4.8‡‡ | 8.6‡ | 14.6 | 10.4 |
| Eczema (past + present) | 22.7 | 12.8‡‡ | 12.2‡‡ | 16.0 | 16.2 |
| Geometric mean IgE (IU/ml) | 208 | 149** | 98*** | 178 | 154 |
| Positive ASE (%) | 55.8 | 43.9‡‡ | 41.8‡‡ | 53.3 | 48.2 |
| Atopic (high IgE or positive ASE) (%) | 65.5 | 54.0‡‡ | 49.2‡‡ | 61.3 | 57.3 |
| Median cytokine level (pg/ml) | | | | | |
| IL-4 | 1.88 | 0.96† | 0.92† | 1.66 | 1.22 (10.2-UD)§ |
| IL-13 | 18.3 | 10.2††† | 7.8††† | 19.1 | 14.2 (45.6-UD) |
| IL-10 | 5.9 | 3.1†† | 2.9†† | 5.9 | 3.9 (10.2-UD) |
| IL-12 | UD | UD | UD | UD | UD |
| IFN-γ | 7.8 | 11.0†† | 13.2†† | 6.4 | 10.5 (23.2-UD) |
| Positive family history within three generations (%) | 54.1 | 49.8 | 49.8 | 48.0 | 51.0 |
| Mean BMI | 21.1 | 22.0 | 21.9 | 21.2 | 21.6 |

**$P < 0.01$, ***$P < 0.001$ on the basis of Student's test. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ on the basis of a median test. ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$ on the basis of $\chi^2$ against group 1, respectively. §Maximum-minimum values.

**Table 2.** Odds ratios for atopy and for occurrence and remission of atopic symptoms in positive versus negative tuberculin responders by age. Multiple logistic analysis was conducted with the SPSSX package, version 2.2. In all models, allowance was made for dichotomized variables including sex, life-style, nutritional status, environmental factors, and family history. Only significant values are shown.

| Tuberculin response | Odds ratio | | |
|---|---|---|---|
| | Atopy | Atopic symptoms | |
| | | Occurrence | Remission |
| Conversion to positive up to 6 years of age | 0.50 (0.29 to 0.83)* | Asthma: 0.31 (0.22 to 0.45)* Eczema: 0.50 (0.33 to 0.91)* | Asthma: 8.2 (6.0 to 9.8)** Eczema: 1.6 (1.0 to 2.2)* |
| Conversion to positive between 6 and 12 years of age | 0.43 (0.25 to 0.83)** | Asthma: 0.42 (0.24 to 0.56)* | Asthma: 6.0 (2.8 to 10.3)*** Eczema: 6.7 (4.8 to 11.4)*** Rhinitis: 9.0 (6.2 to 14.2)*** |

*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$.

IU/ml for children who had a positive tuberculin response at any time, whereas it was 194 IU/ml for children whose responses were always negative. A plot of the logarithm of total serum IgE against the diameter of tuberculin response shows an inverse linear relation, $r = -0.492$ (Fig. 1B). Positive tuberculin responders had significantly lower levels of $T_H2$ cytokines (IL-4, IL-10, and IL-13) and higher levels of the $T_H1$ cytokine IFN-γ.

In tests for confounding variables (*15*), we found no differences in life-style, environmental factors, or nutritional status between the positive and negative tuberculin responders; estimated allergen exposure was similar among the groups with respect to pet animal exposure, character and ventilation of homes, and residence in a rural area. Exposure to helminths, which can promote high IgE levels, was minimal in the population; only 7 of the 867 children showed IgE to *Ascaris lumbricoides*. Similar numbers of positive and negative tuberculin responders reported atopy in any sib, parent, or grandparent (~50%) or had chest radiograph reports of tuberculosis in the same relatives at any time (~13%).

Several lines of evidence suggest that a causal link between tuberculin response and atopy is more likely than fixed determination of both atopy and diminished tuberculin responses by a genetic factor or factors. Our data show that tuberculin responses change, from positive to negative and vice versa, in many children between 6 and 12 years of age (groups 2 and 4 in Table 1). A marked decline in the incidence of positive tuberculin responses in the Wakayama region over a very short genetic interval—95% in 1965, 85% in 1975, 60% in 1985, and 58% in our survey—was accompanied by a decline in infectious clinical cases of tuberculosis from 154.4 per 100,000 in 1974 to 52.1 per 100,000 in 1994 (*17*). Experimental animal data show antigen-independent, reciprocal inhibition of either $T_H1$ or $T_H2$ immunity by infectious agents that strongly promote $T_H1$ responses [such as mycobacteria (*18*)] or $T_H2$ responses [such as schistosomes (*19*)]. The data support the hypothesis that a decline in infection, in this instance tuberculosis, is a factor underlying the rising severity and prevalence of atopic disorders in recent decades in developed countries. These data are also consistent with the idea that atopic responses are limited by $T_H1$ immune mechanisms.

Epidemiological data from Guinea-Bissau show that a history of childhood measles infection around the time of an epidemic was associated with a 50% decrease in the rate of positive atopic skin tests (*20*). In our study, we found no relation between a history of measles infection and atopy. However, there are important population and environmental differences between Wakayama and Guinea-Bissau; also, the Wakayama region has had an established program of measles immunization, with an uptake of 60% or more, and there had been no measles epidemic relevant to our study. It is likely that a set of specific infections that strongly promote $T_H1$ immunity has the potential to inhibit atopic disorder by the repression of $T_H2$ immunity. We believe that the role of such an infection in repressing atopy depends on a number of factors, including its timing, anatomical site, dose, and protractedness; exposure to other infections; and host characteristics such as genetic variables and nutritional status (*21*). Prospective and experimental studies are needed to investigate the action of *M. tuberculosis* and other microorganisms, through natural infection or immunization schedules, in deviating immunity away from atopy.

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14. The regimen in Japan for prevention of tuberculosis to 12 years of age by the Ministry of Health and Welfare was administered as follows. Mantoux skin testing—after single-needle intradermal injection of purified protein derivative (2.5 tuberculin units) of *M. tuberculosis* (Aoyama B strain, Japan BCG Laboratory, Tokyo)—was performed in all children within 3 months of birth, at 6 years of age, and at 12 years of age. Delayed hypersensitivity to tuberculin was categorized as positive (≥10 mm diameter of skin induration after 48 hours), intermediate (5 to 9 mm), or negative. At each of these ages, negative responders were immunized with $10^6$ colony-forming units (CFU) of attenuated bovine *M. tuberculosis* (BCG, Tokyo 172 strain, Japan BCG Laboratory). At 3 months of age, 97 to 98% of the children (groups 1 to 4 in Table 1) were tuberculin-negative and received BCG.
15. T. Shirakawa and K. Morimoto, *Allergy* **48**, 177 (1993); T. Shirakawa *et al.*, *Eur. J. Epidemiol.*, in press. The sample consisted of 867 12- to 13-year-old students (454 boys and 413 girls) at the 18 junior high schools in the southern county of Wakayama prefecture who responded to a questionnaire and donated blood for serology. The questionnaire included details on personal and familial atopic disorders, life-style and environmental characteristics, weight and height, and history of public health immunizations. Nutritional status was assessed as BMI (body mass index), calculated by weight and height. Concentrations of nitrogen dioxide and sulfur dioxide in ambient air have been <0.02 parts per million for the last 30 years in this district. Personal records for skin test responses to tuberculin and BCG inoculation, documented by school doctors, were available from each school's filed records. Diagnoses of asthma, eczema, and rhinitis were made by school doctors on the basis of international criteria. Specific IgE to five airborne allergens and total serum IgE were assayed by Lumiward immunoassay (Shinogi); IgE to *Ascaris lumbricoides* was assayed (Arastat; DPC, Tokyo, Japan). A positive allergen-specific IgE was >0.35 IU/liter. An elevated total serum IgE was taken to be >1 SD above the geometric mean (200 IU/liter). Atopy was defined as one or more positive allergen-specific IgE, a raised total IgE, or both. Serum cytokine levels were immunoassayed in the Mitsubishi Kagaku BCL laboratories (Tokyo) by means of commercial kits; the minimum detectable levels were 0.50 pg/ml for IL-4 and IL-10, 3.1 pg/ml for IL-13, 5 pg/ml for IFN-γ, and 7.8 pg/ml for IL-12 heterodimer. Serum IgE levels were correlated with $T_H2$ cytokine levels (IL-4, correlation coefficient $r = 0.356$; IL-13, $r = 0.565$; IL-10, $r = 0.558$; $P < 0.001$) and were inversely correlated with levels of the $T_H1$ cytokine IFN-γ ($r = -0.567$; $P = 0.001$).
16. N. S. Galbraith, A. Hanson, R. Shoulman, D. W. Andres, D. B. Lee, *Br. Med. J.* **1**, 647 (1972); T. Oettinger, A. Holm, I. M. Mtoni, A. B. Andersen, K. Hasloov, *Infect. Immun.* **63**, 4613 (1995). As a rule, positive tuberculin responses are caused by infection with *M. tuberculosis*, whereas intermediate responses are caused by exposure to nontuberculous mycobacteria or immunization with BCG. We cannot exclude the possibility that some of the conversions to tuberculin positivity after 6 years of age might be attributable to a second immunization with BCG, especially because the Tokyo 172 BCG used is strongly immunogenic, having retained the gene for the major antigen, MPT 64; nor do we know what role environmental mycobacteria may have played in this semirural environment.
17. Japanese Ministry of Health and Welfare, *Trends of Health and Welfare in Japan, 1994* (Ministry of Health and Welfare, Tokyo, 1995).
18. G. B. Mackaness, P. H. Lagrange, T. Ishibashi, *J. Exp. Med.* **139**, 1540 (1974).
19. E. J. Pearce, P. Caspar, J.-M. Grzych, F. A. Lewis, A. Sher, *ibid.* **173**, 159 (1991).
20. S. O. Shaheen *et al.*, *Lancet* **347**, 1792 (1996).
21. R. W. Baker, A. Zumla, G. A. W. Rook, *Q. J. Med.* **89**, 387 (1996); J. M. Grange, *ibid.*, p. 323; P. G. Holt, *Toxicol. Lett.* **86**, 205 (1996).


22. We thank the school doctors of Hidaka Medical Association for help with sample collections, and T. Yamashita and F. Kurimoto (Mitsubishi), T. Onishi (Shinogi), and K. Kato (DPC Japan) for help with serological assays. We thank the students for participating and their teachers and school nurses for their assistance. Supported in part by Mitsubishi Chemical Company (Tokyo).

23 August 1996; accepted 21 October 1996

TO: Jennifer Klein
FROM: Jon Poling
DATE: 10-9-97

RE: Wall Street Journal Article on EPA and Asthma Inhalers

As of 1996, the Clean Air Act banned all production of CFCs (chlorofluorocarbons ) in accordance with the Montreal Protocol, an international agreement to protect the ozone layer. However, the United States successfully argued for an "essential use exemption" that allows for enough domestic production of CFCs to meet the needs of American asthmatics. These exemptions last until 1999 and cover all Metered Dose Inhalers (MDIs) that are CFC based.

There is one CFC-free inhaler on the market, but it is not an adequate substitute for the CFC based inhalers. The International Pharmaceutical Aerosol Consortium estimates that 11 new CFC-free inhalers will be on the market by the year 2000. Until that time, the EPA will keep the CFC based inhalers exempt from the Montreal Protocol Ban.

Jen - FYI

Jon - Check to see if this happened. Gather info on what we are doing to fight asthma. Jen

# EPA to Asthmatic Kids: Hold Your Breath

By Robert M. Goldberg

Today, the Clinton administration will issue a proposal that could take away asthma inhalers from inner-city children to protect the Earth's ozone layer.

This is not a sick joke, or the product of an overheated conservative imagination. Rather, the Environmental Protection Agency wants to announce a ban on chlorofluorocarbon-powered inhalers in Montreal at the international meeting on ozone protection as a shining symbol of America's international environmental stewardship. Never mind that such a ban would increase the cost and difficulty of treating childhood asthma, and that inner-city children are already six times more likely than other children to die because of inadequate asthma care. Even though such inhalers account for less than 1.5% of total CFC emissions world-wide, the EPA is likely to get its wish.

Under the Montreal protocol on ozone-depleting substances, 155 countries have agreed to phase out production of CFCs and other ozone-depleting substances. An amendment to the protocol introduced by the U.S. in 1990 accelerated the international phase-out. However, that amendment left one important feature of the protocol intact. It still allows each member country to exempt from the ban certain CFC-containing products deemed "essential." Since the treaty was ratified, asthma inhalers have been exempt because of their public health importance. And each year, the EPA nominates other products for exemption. This time around, however, the EPA wants to tell the world it will no longer ask to exempt inhalers.

EPA Administrator Carol Browner says that the goal of the ban, like her many other environmental initiatives, is to ensure that U.S. children are protected from environmental health risks. Ms. Browner claims that more environmental regulations will protect asthmatic children most of all, since they are among the most vulnerable to environmental threats. Hence, taking asthma inhalers away from children is being done in the name of children's health.

It's true that non-CFC asthma products do exist, and that some work better than those containing CFCs. But different patients' asthma symptoms respond differently to each of the available medicines, and specialists are opposed to reducing that range of products simply for the sake of environmental correctness. In addition, poorer children are especially reliant on generic inhalers with CFC propellants, which can cost one-eighth the price of newer brand-name products without CFCs. Ultimately, these two factors contribute to the fact that only half of all children are following the inhalation schedule necessary to keep their asthma under control. An expert panel of the National Institute for Allergies and Infectious Diseases found in 1995 that failure to comply with treatment explains the 300% increase in asthma-related deaths among children between 1980 and 1993.

Why would the EPA want to hasten the elimination of a medicine that's essential to keeping kids alive? The Montreal protocol doesn't require it. And a large number of member countries are opposed to such a quick phase-out.

Yet the EPA wants America to be the first country to develop a solution for the elimination of CFC-powered inhalers. So, despite resistance from doctors, the EPA has pushed the Food and Drug Administration for tougher regulations. Under the proposed new FDA rules, if one CFC-free inhaler hits the market, any CFC-powered inhaler delivering the same medicine would have to go. In this way, all those who use CFC inhalers—about 95% of asthma inhaler users—will be deprived of the opportunity to use the inhaler that works best for them.

Dozens of medical groups and hundreds of allergists have urged the FDA not to go ahead with its planned termination, pleading that a change in medicine will compromise children's health. The Joint Council of Allergy, Asthma and Immunology has told both the FDA and the EPA that their proposal will unfairly punish poor children and the elderly, who have the highest risk of asthma-related sickness and death. Even the FDA panel that made this proposal expressed concerns about the impact on such children of wiping out a whole class of CFC-powered inhalers.

The question is why the EPA is willing to invite those consequences. In a letter to the FDA, the EPA claimed that the U.S. is forced under the terms of the Montreal protocol to limit exemptions to cases where no non-CFC substitutes are available. Since CFC-free devices do exist, the EPA argues, the ban must apply. The EPA objects to the FDA's intention to weigh the benefits of reducing CFC emissions compared to the negative effects for asthmatics. Incredibly, the EPA wrote to the FDA that domestic assessments of impact cannot be considered in the FDA's decisions if they conflict with U.S. treaty obligations. In other words, the FDA cannot consider the health impact of a ban on CFC-powered inhalers on U.S. children because it is at odds with the EPA's desire to demonstrate America's commitment to environmental vigilance.

Worse, even as the EPA is hell-bent on snatching asthma inhalers away from children and the elderly, it had no problem exempting other products that have nothing to do with children's health. Among the other CFC-laden products the EPA has decided not to ban: document-preservation sprays and foam insulation for coaxial cable. It has also spared CFC-emitting fire extinguishers even though the EPA found some alternatives are already on the market and in use. The EPA's Ms. Browner apparently believes that preservation sprays and coaxial cable are more important than medicine for asthmatic children.

This is what we have come to expect from the Clinton administration: Children are shamelessly invoked as a justification, even for policies that hurt children. When it comes to their inhalers—well, what's a few innocent lives, particularly of children in the inner city, compared to President Clinton's goal of showing international leadership on environmental protection? If children lose access to inhalers, they'll just have to hold their breath until the ozone layer is repaired.

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*Mr. Goldberg is a senior research fellow at the Center for Neuroscience, Medical Progress and Society, George Washington University.*

THE WALL STREET JOURNAL FRIDAY, SEPTEMBER 19, 1997

**Background on the Montreal Protocol Ban on CFCs**

- Metered Dose Inhalers (MDIs) are medical devices used to treat asthma. Most MDIs now use chlorofluorocarbons (CFCs) to propel the medication in the inhaler. In 1996, the Clean Air Act banned production of CFCs, pursuant to the Montreal Protocol, an international agreement to protect the ozone layer.

- EPA did not announce a ban on CFC-based MDIs at the Meeting of the Parties to the Montreal Protocol held September 8 -19 1997. By contrast, the U.S. successfully argued for "essential use exemptions" from the ban in 1996, 1997, 1998 and 1999, in order to allow for domestic production of enough CFCs to meet the needs of American asthmatics.

- While a CFC-free inhaler is currently on the market, it does not adequately substitute for the many different types of MDIs now in use. The International Pharmaceutical Aerosol Consortium estimates that 11 new CFC-free inhalers will be available by the year 2000, and as many as 35 by 2005. EPA will continue to ask for necessary exemptions from the Montreal Protocol ban on CFC production until a transition from CFC-based to CFC-free inhalers occurs in the U.S.

- Progress in protecting the ozone layer will not come at the expense of other important public health concerns, like asthma. EPA has worked closely with the FDA to craft a transition process that ensures health protection of all MDI users. Over time, the availability of substitutes will provide several options for American asthmatics while protecting public health and the ozone layer.

**EPA Actions to Fight Asthma in Children**

- In July 1997, EPA Administrator Carol M. Browner signed updated air quality standards for ozone and particulate matter to better protect American children from the harmful effects of air pollution. These new standards will provide new health protections to 35 million children, by helping to prevent 15,000 premature deaths, about 350,000 cases of aggravated asthma and nearly a million cases of decreased lung function.

- Working in partnership with the National Parent Teachers Association, the National Education Association, the American Federation of Teachers and the American Lung Association, EPA has developed the *Indoor Air Quality Tools for Schools* Action Kit, an easy-to-use guide which describes simple, low-cost methods for schools to improve their indoor air quality and, thereby, reduce environmental asthma risks to children.

- By integrating the American Lung Association's "Open Airways" children's asthma management curricula and EPA's *Indoor Air Quality Tools for Schools* program, the "Open Airways for Schools" program focuses on developing asthma management skills for high-risk, inner city minority children who have a higher than average asthma death rate.

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**THE NEW YORK CHILDHOOD ASTHMA INITIATIVE**
**Revised Preliminary Scope of Work**

This city wide initiative is designed to address a growing health crisis with respect to childhood asthma. Organized as a partnership between the office of Councilman Ken Fisher and The Children's Health Fund (CHF), with strong collaboration with the New York City Department of Health, the program will have the following goals and program components.

## I. GOALS

1. Increase in public awareness and knowledge of pediatric asthma
2. Development of innovative primary care programs with a special asthma focus
3. Development of a broad, system-based model that integrates community, medical, educational and other interventions to address the childhood asthma epidemic
4. Development of sustainable public policies and programs that will contribute to the ongoing reduction of childhood asthma morbidity and the elimination of childhood deaths due to asthma

## II. PROGRAM DEVELOPMENT PROCESS

The program will be developed through a process that will a) give program attention to specific communities with high asthma prevalence and to special populations with high asthma prevalence, and b) ensure coordination with and be complementary to current asthma-related activities of the NYC DOH, as well as asthma-related activities of other institutions, agencies and organizations, and c) consult and collaborate with community organizations in targeted, high prevalence communities on program development, implementation and potential for sustainability.

An initial collaborative planning meeting will be scheduled with representatives from Councilman Fisher's office, the Children's Health Fund and the NYC DOH, chaired by Councilman Fisher and Irwin Redlener, MD, to discuss program design, implementation and potential community linkages. Specific topics will include a) the development of criteria for the identification of high prevalence communities / special populations as well as the site selection process, and b) the coordination of New York Childhood Asthma Initiative program components with current DOH activities, especially those in the Hunts Point area. The discussion of overall program design for the Childhood Asthma Initiative will also include contributions of the experience of the NYC DOH in Hunts Point, as well as the experience of other asthma programs and population-based models, both in NYC and elsewhere.



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## III. PROGRAM COMPONENTS

A. Establishment of a Childhood Asthma Task Force

Co-chaired by Councilman Fisher and CHF President Irwin Redlener, MD, the task force will be composed of representatives of NYC agencies, organizations, unions, and individuals with relevant experience in a wide range of service sectors. The Task Force may appoint subcommittees as needed.

Potential Tasks:

1. Participation in the development of a major asthma awareness campaign focused on the epidemic of childhood asthma in NYC

2. Development of appropriate public policy responses to the epidemic of childhood asthma

B. Childhood Asthma Awareness Campaign

This campaign is designed to call significant public attention to the new crisis in pediatric asthma. Its purpose will be to inform the public, provide essential information to parents of children with asthma, educate children with asthma about their disease and offer state-of-the-art information on asthma diagnosis and treatment to primary care providers who deal with this condition. It will be designed to develop effective asthma educational models to train a wide range of service providers, agencies and community organizations that interact with children. An important anticipated outcome of the Childhood Asthma Initiative will be the development of successful models of health education around asthma that may also be applied to other health conditions.

Possible Campaign Components:

1. Public Information Initiative: This component will include the development of asthma awareness and knowledge surveys, the development of an ad campaign, public service announcements, the development of media coverage and appropriate materials for general distribution. These materials might include Asthma Information Kits for children and parents, community organizations such as churches and other religious institutions, tenants associations, block associations, local businesses and community service organizations; Asthma Fact Sheets for distribution at health fairs, local businesses and community events as well as other asthma information materials. The targeted audience for the public information initiative would include parents and caretakers of children with asthma, children and adolescents with asthma, community organizations, residents of high-risk communities, special populations with high asthma prevalence rates such as homeless children, and the general population. The public campaign would also



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publicize the "asthma information hotline" and other aspects of this program. Development of the public information initiative will be in coordination with the health promotion activities of the NYC DOH and other asthma education efforts in the NYC area.

2. Asthma Information Hotline: This component will be directed at provision of state-of-the-art information on asthma for parents, teachers, community organizations, agencies and others as well as enhancing the participation of parents in the management of asthma for their children. Information will be linguistically and culturally appropriate. The hotline will have an 800 number available 5-7 days a week. It will offer general information about asthma, prevention of asthma attacks and advice on how and where to secure a primary care provider with appropriate expertise in asthma management.

3. Provider Education: In New York City currently, provider knowledge with respect to asthma diagnosis and management is variable and inconsistent. The recent release of the revised Guidelines for the Diagnosis and Management of Asthma (National Asthma Education and Prevention Program, NHLBI) offers an opportunity to develop provider education strategies that reflect state-of-the-art asthma care. Under this component of the program, an effort will be undertaken to educate physicians, as well as other primary care providers such as nurses and physician assistants. Other professionals that interact regularly with asthmatic children and their parents will also be targeted, including clerks at health facilities, pharmacists and social service providers. A particular focus will be those providers who provide services in high risk communities and those serving high risk special populations. The provider education programs will be coordinated with existing efforts that target provider education under the auspices of DOH and other organizations in the city.

   Provider education strategies will identify effective approaches and will be designed to complement current programs, such as the Greater New York Asthma Initiative Provider Education Conference scheduled for Spring, 1998. It may also include:

   - the organization of a city-wide conference on childhood asthma
   - development of targeted teaching programs and educational materials for physicians
   - a physician's newsletter
   - the development of special training programs for nurses, pharmacists, social service workers and clerical staff

   The provider education programs will include information on the diagnosis of asthma, identification of asthma symptoms, identification of asthma triggers, identification of risk factors for fatal asthma, current treatment options, prevention strategies, development of patient-provider asthma management plans, and



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appropriate use of asthma management devices such as peak flow meters and spacers.

4. Enhanced School and Day Care Programs: This component will focus on educating school-age children and adolescents with asthma about asthma triggers, asthma management, asthma medications, strategies for maximal asthma control, asthma and athletics and reduction in activity limitation due to asthma. It will also focus on educational programs for teachers, administrators and other school staff. It will build on school-based programs already existing in the city and will be targeted towards high-risk school districts.

   The Day Care program would provide education to both day care staff and parents in the recognition of asthma symptoms, use of asthma medications, identification of asthma triggers, general asthma management strategies and identification of primary care resources. It will also include specific early childhood development programs such as Head Start.

C. Clinical Program: **Primary Care and Asthma Centers**

Possible Program Components:

1. Establishment and/or enhancement of primary care programs with a special asthma focus: Primary Care and Asthma Centers will be organized in two communities where asthma is particularly problematic. Locations will include the Hunts Point Peninsula community where The Children's Health Fund's affiliated project, the South Bronx Children's Health Center, is already working closely with the New York City Department of Health. This program will be structured to complement existing asthma initiatives in the Hunts Point community. An additional Primary Care and Asthma Center site will be established in collaboration with institutions that currently provide primary health care services in Brooklyn. On-going development of this program component will be closely coordinated with the Department of Health and local community partners such as The Point. The Primary Care and Asthma Centers will provide needed state-of-the-art asthma care in these two high-risk communities and will also serve as demonstration sites for the development and evaluation of a range of clinical, educational and community programs and materials targeted at childhood asthma for broader implementation and dissemination.

   **Neighborhood Asthma Specialists:** A critical component of the childhood asthma initiative will be the integration of increased public awareness of asthma with the provision of enhanced clinical care. As part of this effort, nurses would be trained to become neighborhood-based specialists in asthma management and education. They would be initially based in the Primary Care and Asthma Centers described below and would provide asthma education, training and outreach across a wide range of sites within a specific geographic area, linking medical facilities to schools,



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housing, community organizations, churches, tenant associations, day care centers, multi service centers, block associations, local social service organizations, local pharmacies, local businesses and others providing community services. The Neighborhood Asthma Specialists would thus serve a key role in integrating and linking asthma education and services within high-risk geographic locations and in developing a sustainable focus on childhood asthma within those communities. A particular component of their community education activities would be the identification and training of key neighborhood residents to become Neighborhood Asthma Educators. This program component will be initially developed as part of the Primary Care and Asthma Centers; additional Neighborhood Asthma Specialists may also be based in other high risk communities. In Hunts Point, the Neighborhood Asthma Specialists will coordinate with ongoing activities of the NYC DOH.

2. High prevalence special population emphasis: This program component will focus on special population subgroups with high asthma prevalence rates, including homeless children, children under detention, street youth, immigrant children and high-risk age groups such as infants, very young children, and teen parents.

3. Other clinical enhancement programs and asthma interventions: Interventions that could be developed and evaluated in high-risk communities, either as pilot programs or smaller-scale components of the main program, include the development of generalizable models for short-term intensive asthma interventions, the use of mobile units to supplement fixed site programs in additional sites for clinical or educational purposes and the development of interventions to reduce environmental and psychosocial risk factors for asthma attacks.

## IV. EVALUATION

A specific evaluation plan will be developed for each program component to assess its effectiveness, generalizability, and potential for sustainability and expansion. The program -specific evaluation plans will be developed in consultation with other asthma-related programs in NYC that have similar program components to ensure effective linking of evaluation results across programs. In particular, evaluation of program components that are situated in the Hunts Point community will be coordinated with existing programs of the NYC DOH. As part of an evaluation baseline assessment, a targeted assessment of childhood asthma prevalence and incidence in NYC could be undertaken. This could include the identification of communities, age groups and special populations with high asthma prevalence rates, assessment of indicators of asthma morbidity (e.g. hospitalizations, emergency department use, primary care visits, days missed from school because of asthma), and surveillance / investigation of near-fatal asthma attacks and asthma deaths. Surveillance efforts will be coordinated with and will collaborate with other surveillance efforts, in particular those of the NYC DOH and others around emergency department asthma surveillance. The evaluation plan will also serve to identify new directions for the New York Childhood Asthma Initiative and suggest modifications of the existing program.



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**DRAFT** 091597 11:58

# THE PROPOSED PLAN TO ANNOUNCE THE NEW YORK CITY CHILDHOOD ASTHMA INITIATIVE

WHAT: A press conference for **The Children's Health Fund** to announce a major public health initiative, **The New York City Childhood Asthma Initiative**, and plans to develop a **primary care and asthma center**. This is an opportunity to unveil the program components, to talk with principals involved, and dignitaries who support the initiative as an effort to fight against the epidemic of asthma. This comprehensive plan is designed to be a model for programs that can be executed throughout the United States.

WHO: An exceptional coalition of:

- **FEDERAL INTERESTS**: The White House, Ms. Hillary Rodham Clinton;
- **LOCAL GOVERNMENT**: The City Council of New York, led by Councilman Kenneth Fisher;
- **PUBLIC HEALTH ADMINISTRATION**: the New York City Department of Health, represented by Benjamin Mojica, Acting Commissioner;
- **THE CHILDREN'S HEALTH FUND**: spearheaded by Irwin Redlener, MD;
- **ACADEMIC HEALTH CENTER**: Montefiore Medical Center, represented by Spencer Forman, MD, Chief Executive Officer;

WHY: The New York City Childhood Asthma Initiative addresses the epidemic proportions of asthma in New York City, where incidence of the disease is among the highest in the nation. The press conference is to advise the community, via the press, of the diverse efforts that the Initiative will introduce, and to introduce the plan as a national model.

WHEN: Monday, September 22, 1997
1:00 pm
Time frame: approximately 20 minutes to one-half hour;

Post-conference: visit to nearby day care center .

WHERE: South Bronx Children's Health Center
911 Longwood Avenue
The Bronx, New York.

OTHER:

**1.0 Speakers**

1.1 Irwin Redlener, MD, President, The Children's Health Fund;
1.2 Kenneth Fisher, Councilman, Borough of Brooklyn;
1.3 Benjamin Mojica, MD, Acting Commissioner, NYC Department of Health;
1.4 Spencer Forman, MD, President, Chief Executive Officer, Montefiore Medical Center;
1.5 Hillary Rodham Clinton, Esq., First Lady of the United States.

2.0 Other invited, nonspeaking guests to be acknowledged, including New York City Council President Peter Vallone, Bronx Borough President Frederic Ferrer, U.S. Representative Jose Serrano, Bronx Assemblyman Jeffrey Klein, private sector major donation from the President of Schering Laboratories (full list to follow.)

**3.0 Tentative Agenda**

| | |
|---|---|
| 1:00 | Scheduled start time |
| 1:00 | Irwin Redlener, MD opens the floor, introduces Mrs. Clinton, introduces other speakers, invites Ken Fisher to speak. |
| 1:01 | Kenneth Fisher discusses the genesis of the budget allocation for the New York City Childhood Asthma Initiative. |
| 1:05 | Irwin Redlener speaks of the problems of underserved children, asthma and the need for a children's agenda in New York City. |
| 1:09 | Benjamin Mojica, Acting Commissioner of Health, presents the Department's perspectives on the program. |
| 1:13 | Spencer Forman, Montefiore Medical Center, speaks of the initiative from the perspective of the incidence of asthma in the Bronx, and Montefiore's long-term commitment to children's health. |
| 1:17 | Hillary Rodham Clinton speaks. (CHF to be advised of her point of view.) |
| 1:21 | Conclusion. |
| 1:22 | Questions and answers. |

→ Call re Speakers

30% uninsured
65% Medicaid
15% Third party insurance

2 pieces:
(1) Clinical Services
(2) Public Awareness

65% Hispanic
30-35% Af-Am.

Many eligible for Medicaid, but not enrolled

CC: Sanjay Gupta

4pgs 9/22

CC Daniels

THE WHITE HOUSE
WASHINGTON

**OFFICE OF THE FIRST LADY**

57234

TO Patti Solis - Doyle

FROM Jen

FAX # 6-5340

PHONE #

# OF PAGES (including cover)

COMMENTS As I said, the event could include:

(1) A visit to the clinic in Hunt's Point (which has the highest asthma rate in the country); and

(2) A visit to a child care center in Hunt's Point where they will be training child care providers about asthma.

Irwin has all commitments ($) in place for this project (except for contribution from Schering-Plough which they expect soon). This event would be the launch of the initiative.

Jen

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## THE NEW YORK CHILDHOOD ASTHMA INITIATIVE
### Revised Preliminary Scope of Work

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## I. GOALS

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## II. PROGRAM DEVELOPMENT PROCESS

The program will be developed through a process that will a) give program attention to specific communities with high asthma prevalence and to special populations with high asthma prevalence, and b) ensure coordination with and be complementary to current asthma-related activities of the NYC DOH, as well as asthma-related activities of other institutions, agencies and organizations, and c) consult and collaborate with community organizations in targeted, high prevalence communities on program development, implementation and potential for sustainability.

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## III. PROGRAM COMPONENTS

A. Establishment of a Childhood Asthma Task Force

Co-chaired by Councilman Fisher and CHF President Irwin Redlener, MD, the task force will be composed of representatives of NYC agencies, organizations; unions, and individuals with relevant experience in a wide range of service sectors. The Task Force may appoint subcommittees as needed.

Potential Tasks:

1. Participation in the development of a major asthma awareness campaign focused on the epidemic of childhood asthma in NYC

2. Development of appropriate public policy responses to the epidemic of childhood asthma

B. Childhood Asthma Awareness Campaign

This campaign is designed to call significant public attention to the new crisis in pediatric asthma. Its purpose will be to inform the public, provide essential information to parents of children with asthma, educate children with asthma about their disease and offer state-of-the-art information on asthma diagnosis and treatment to primary care providers who deal with this condition. It will be designed to develop effective asthma educational models to train a wide range of service providers, agencies and community organizations that interact with children. An important anticipated outcome of the Childhood Asthma Initiative will be the development of successful models of health education around asthma that may also be applied to other health conditions.

Possible Campaign Components:

1. Public Information Initiative: This component will include the development of asthma awareness and knowledge surveys, the development of an ad campaign, public service announcements, the development of media coverage and appropriate materials for general distribution. These materials might include Asthma Information Kits for children and parents, community organizations such as churches and other religious institutions, tenants associations, block associations, local businesses and community service organizations; Asthma Fact Sheets for distribution at health fairs, local businesses and community events as well as other asthma information materials. The targeted audience for the public information initiative would include parents and caretakers of children with asthma, children and adolescents with asthma, community organizations, residents of high-risk communities, special populations with high asthma prevalence rates such as homeless children, and the general population. The public campaign would also



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publicize the "asthma information hotline" and other aspects of this program. Development of the public information initiative will be in coordination with the health promotion activities of the NYC DOH and other asthma education efforts in the NYC area.

2. Asthma Information Hotline: This component will be directed at provision of state-of-the-art information on asthma for parents, teachers, community organizations, agencies and others as well as enhancing the participation of parents in the management of asthma for their children. Information will be linguistically and culturally appropriate. The hotline will have an 800 number available 5-7 days a week. It will offer general information about asthma, prevention of asthma attacks and advice on how and where to secure a primary care provider with appropriate expertise in asthma management.

3. Provider Education: In New York City currently, provider knowledge with respect to asthma diagnosis and management is variable and inconsistent. The recent release of the revised Guidelines for the Diagnosis and Management of Asthma (National Asthma Education and Prevention Program, NHLBI) offers an opportunity to develop provider education strategies that reflect state-of-the-art asthma care. Under this component of the program, an effort will be undertaken to educate physicians, as well as other primary care providers such as nurses and physician assistants. Other professionals that interact regularly with asthmatic children and their parents will also be targeted, including clerks at health facilities, pharmacists and social service providers. A particular focus will be those providers who provide services in high risk communities and those serving high risk special populations. The provider education programs will be coordinated with existing efforts that target provider education under the auspices of DOH and other organizations in the city.

Provider education strategies will identify effective approaches and will be designed to complement current programs, such as the Greater New York Asthma Initiative Provider Education Conference scheduled for Spring, 1998. It may also include:

- the organization of a city-wide conference on childhood asthma
- development of targeted teaching programs and educational materials for physicians
- a physician's newsletter
- the development of special training programs for nurses, pharmacists, social service workers and clerical staff

The provider education programs will include information on the diagnosis of asthma, identification of asthma symptoms, identification of asthma triggers, identification of risk factors for fatal asthma, current treatment options, prevention strategies, development of patient-provider asthma management plans, and



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appropriate use of asthma management devices such as peak flow meters and spacers.

4. Enhanced School and Day Care Programs: This component will focus on educating school-age children and adolescents with asthma about asthma triggers, asthma management, asthma medications, strategies for maximal asthma control, asthma and athletics and reduction in activity limitation due to asthma. It will also focus on educational programs for teachers, administrators and other school staff. It will build on school-based programs already existing in the city and will be targeted towards high-risk school districts.

   The Day Care program would provide education to both day care staff and parents in the recognition of asthma symptoms, use of asthma medications, identification of asthma triggers, general asthma management strategies and identification of primary care resources. It will also include specific early childhood development programs such as Head Start.

C. Clinical Program: **Primary Care and Asthma Centers**

Possible Program Components:

1. Establishment and/or enhancement of primary care programs with a special asthma focus: Primary Care and Asthma Centers will be organized in two communities where asthma is particularly problematic. Locations will include the Hunts Point Peninsula community where The Children's Health Fund's affiliated project, the South Bronx Children's Health Center, is already working closely with the New York City Department of Health. This program will be structured to complement existing asthma initiatives in the Hunts Point community. An additional Primary Care and Asthma Center site will be established in collaboration with institutions that currently provide primary health care services in Brooklyn. On-going development of this program component will be closely coordinated with the Department of Health and local community partners such as The Point. The Primary Care and Asthma Centers will provide needed state-of-the-art asthma care in these two high-risk communities and will also serve as demonstration sites for the development and evaluation of a range of clinical, educational and community programs and materials targeted at childhood asthma for broader implementation and dissemination.

   **Neighborhood Asthma Specialists:** A critical component of the childhood asthma initiative will be the integration of increased public awareness of asthma with the provision of enhanced clinical care. As part of this effort, nurses would be trained to become neighborhood-based specialists in asthma management and education. They would be initially based in the Primary Care and Asthma Centers described below and would provide asthma education, training and outreach across a wide range of sites within a specific geographic area, linking medical facilities to schools,



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housing, community organizations, churches, tenant associations, day care centers, multi service centers, block associations, local social service organizations, local pharmacies, local businesses and others providing community services. The Neighborhood Asthma Specialists would thus serve a key role in integrating and linking asthma education and services within high-risk geographic locations and in developing a sustainable focus on childhood asthma within those communities. A particular component of their community education activities would be the identification and training of key neighborhood residents to become Neighborhood Asthma Educators. This program component will be initially developed as part of the Primary Care and Asthma Centers; additional Neighborhood Asthma Specialists may also be based in other high risk communities. In Hunts Point, the Neighborhood Asthma Specialists will coordinate with ongoing activities of the NYC DOH.

2. High prevalence special population emphasis: This program component will focus on special population subgroups with high asthma prevalence rates, including homeless children, children under detention, street youth, immigrant children and high-risk age groups such as infants, very young children, and teen parents.

3. Other clinical enhancement programs and asthma interventions: Interventions that could be developed and evaluated in high-risk communities, either as pilot programs or smaller-scale components of the main program, include the development of generalizable models for short-term intensive asthma interventions, the use of mobile units to supplement fixed site programs in additional sites for clinical or educational purposes and the development of interventions to reduce environmental and psychosocial risk factors for asthma attacks.

## IV. EVALUATION

A specific evaluation plan will be developed for each program component to assess its effectiveness, generalizability, and potential for sustainability and expansion. The program -specific evaluation plans will be developed in consultation with other asthma-related programs in NYC that have similar program components to ensure effective linking of evaluation results across programs. In particular, evaluation of program components that are situated in the Hunts Point community will be coordinated with existing programs of the NYC DOH. As part of an evaluation baseline assessment, a targeted assessment of childhood asthma prevalence and incidence in NYC could be undertaken. This could include the identification of communities, age groups and special populations with high asthma prevalence rates, assessment of indicators of asthma morbidity (e.g. hospitalizations, emergency department use, primary care visits, days missed from school because of asthma), and surveillance / investigation of near-fatal asthma attacks and asthma deaths. Surveillance efforts will be coordinated with and will collaborate with other surveillance efforts, in particular those of the NYC DOH and others around emergency department asthma surveillance. The evaluation plan will also serve to identify new directions for the New York Childhood Asthma Initiative and suggest modifications of the existing program.



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MEMORANDUM FOR THE FIRST LADY Sep 10, 1997

FROM: Domestic Policy Staff

SUBJECT: Child Asthma Initiative

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IMPACT

Asthma is a chronic inflammatory disease of the airways. In the United States, asthma affects 14 to 15 million persons. It is the most common chronic disease of childhood, affecting an estimated 4.8 million children with the direct and indirect cost estimated at $6.2 billion dollars in 1993. Over 3800 children and young adults under 25 died from asthma nationwide during the period 1980-1993. 342 children died from asthma in 1993 alone. Asthma is associated with the loss of 28 million activity days annually and 2.2 million pediatrician visits. It is the leading cause of school absenteeism. It has been estimated that among children 5-17 years old, asthma accounted for approximately 10 million missed school days at a cost of $726.1 million in caretakers' time lost from work.

TRENDS

The burden of asthma on the US population is increasing. Through the 1980's, the prevalence of asthma increased 29%, hospitalization rates increased 6% and mortality rates increased as well. The most notable increases were for children and young adults. Hospitalization rates for children less than five years old have increased 57% since 1980. These rates increased at a time when total hospitalization rates for children decreased. Overall, the annual age-specific asthma death rate increased 118% (from 1.7 to 3.7 per million) between 1980 and 1993 for persons aged 0-24. Explanations for rising prevalence, morbidity and mortality are varied. Investigators have attributed increased hospitalization to improved diagnosis, untoward effects of treatment, environmental factors, improvements in vital statistic reporting, and increased tendencies for asthmatic patients to use hospital emergency departments as primary sources of care.

VULNERABLE POPULATIONS

Childhood asthma has become more prevalent and more severe in the last decade, and disproportionately affects minority populations. In 1993, among children aged 5-14 years, blacks were four times more likely than whites to die from asthma.. In the 0-4 age group, blacks were six times more likely to die from asthma than whites. Hospitalization rates are consistently highest among blacks. In 1993, among persons aged 0-24 years, blacks were 3.4 times more likely than whites to be hospitalized for asthma..

Children living in the inner city are particularly vulnerable. New York City has the highest rate of hospitalization and mortality for childhood asthma of any area in the United States. As of 1993, New York City children were hospitalized for asthma at four times the national rate. Within the city, these rates are three to five times higher for African Americans and Latinos than for the rest of the population. Areas in New York City with the highest asthma hospitalization rates include the South Bronx, Upper Manhattan, Central and North Brooklyn. Nationally, asthma rates are highest in New york, Chicago, Fresno, and Maricopa County, Arizona.

The exact relationship between generally known risk factors and the increase in asthma-related morbidity and mortality among minority inner city children has not been determined. Poverty undoubtedly impacts upon the health of inner-city populations. Poverty has been linked to underdiagnosis and subsequent reduced preventive asthma care. Defined risk factors such as passive and active cigarette smoking and air pollution may be greater for minority, inner-city children. Also, infestation with pests such as roaches, mites, rodents and mosquitoes are greater problems among the poor than the more affluent. Finally, socio-economic status has been directly linked to overall compliance and medical follow-up.

PATHOGENESIS AND MANAGEMENT

Asthma results from complex interactions among inflammatory cells, mediators and the cells and tissues resident in the airway. Atopy, the genetic predisposition for the development of a mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma. In susceptible individuals, this chronic inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness

and cough, particularly at night and in early morning. The episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or with treatment. This inflammation does cause an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

The effective treatment of asthma is dependent on four components: 1) correct diagnosis of asthma 2) reducing factors contributing to asthma severity 3) pharmacological therapy 4) self-management education. The goals of asthma therapy are to: 1) prevent chronic and troublesome symptoms 2)maintain normal pulmonary function 3) maintain normal activity levels 4)prevent recurrent exacerbations 5) provide optimal pharmacotherapy with minimal side-effects and 6) meet patients' and families' expectations of satisfaction with asthma care.

NEW YORK CHILDHOOD ASTHMA INITIATIVE

This initiative is organized as a partnership between the office of Councilman Ken Fisher and The Children's Health Fund, with strong collaboration from the New York City Department of Health. The goals of the program are to increase public awareness and knowledge of pediatric asthma and develop programs, models, and policies that will serve to reduce childhood asthma morbidity and eliminate childhood deaths due to asthma. The initiative will give attention to specific communities with high asthma prevalence.

The program components will include a Childhood Asthma Task Force. This task force will be representative of NYC service sector agencies and will be co-chaired by Councilman Fisher and Children's Health Fund President Irwin Redlener MD. Other program components are Childhood Asthma Awareness Campaign and Clinical Programs. These components will include a public information initiative, asthma information hotline and provider education. In addition, the establishment and/or enhancement of primary care programs with special asthma focus will be organized in two communities where asthma is particularly problematic, Hunt's Point and Brooklyn. Existing care centers will provide needed state-of-the-art asthma care in these two high risk communities and will serve as demonstration sites for a range of clinical and educational programs targeted at childhood asthma.

TO: Tom Freedman

FROM: Neera Tanden

RE: Asthma

---

**The Problem:**

There has been a huge increase in asthma over the last decade. It is a particular problem for children. While there has been a great deal of speculation as to the cause of the dramatic increase, no one can figure out why it is happening. The speculation runs the gamut from environmental pollution to tobacco to urban violence.

Asthma is actually a problem throughout the developed world; people are suffering asthmatic reactions to a range of allergens that once caused little trouble. And basically, although scientists are learning more about asthma, the explosion is still largely a mystery.

**The Facts**

- Asthma now afflicts about 14.6 million Americans.[Newsweek, 5/26/97] This is **twice** the number it was 25 years ago.[Life, 5/97]
- The number of American asthmatics grew by 6.2 million between 1984 and 1994 -- an astonishing **74%** increase. [San Francisco Chronicle, 7/3/96]
- There are now more than 5 million children afflicted with asthma - 1 in 13 children in 1993, which is 79% more than in 1982.[LA Times, 10/27/96]
- Asthma costs $ 6.2 billion a year in missed work and school, in medications and hospital visits.[Life, 5/97]
- Asthma has become the most common chronic disease of childhood, the No. 1 cause of hospitalization and absenteeism.[Life, 5/97]
- Asthma is especially severe in the inner city, where rates of asthma emergency room visits and deaths can be eight times the national average.
- The United States has an overall asthma rate of about 5 percent. But the rate is 8.4 percent in New York City, and it can reach 25 percent among kids in the poorest urban neighborhoods.

**The Interest:**

The dramatic rise in asthma has been called an "epidemic," "pandemic," and "crisis" in recent media stories.

1. Newsweek, "The Scary Spread of Asthma" (Cover Story), 5/26/97

2. Good Morning America

3. The Today Show

4. Life Magazine, "An Epidemic of Sneezing and Wheezing," 5/97

5. Front page: LA Times, San Francisco Chronicle, NY Daily News

**The Tie-In**

Asthma is related to three policy proposals the Administration is currently pushing. Generating interest in fighting asthma will only help increase support for these proposals.

1. New EPA regulations --
We have used asthma as a major justification for our plan to increase environmental regulations. In fact, during the briefing on the new standards, Katie McGinty said:

"[T]he President is strengthening current smog standards that we know seriously exacerbate asthma conditions and other lung ailments, and that particularly affect children. Asthma is one of the leading causes of children's hospitatlization and, following from that, a leading cause of children missing out on school days. So the step -- the decision the President made today advances our commitment to clean air in this country and allows ust ot take important gains on a pullutant that we konw causes premature death and other pullutants that we know dramatically exacerbate lung conditions and particularly asthma."

We are and should continue to highlight the fact that we are proposing these regulations simply to lower the number of children who suffer from asthma.

2. Expanding Health Care for Children

Because asthma is the number one chronic disease in children and the number one cause of hospitalization, it is a big reason why we need to insure these children whose parents are working but cannot afford health care. If asthmatic children have regular access to medical care, their asthma can be regulated and controlled, thereby lessening the number of emergency room visits.

3. Tobacco

Smoking - especially by parents near their children - can cause asthma. And of course, asthmatics suffer greatly from those who smoke around them because their smoke can often trigger an attack.

**The Proposals**

1. Researching the Causes of Asthma. We basically do not know why rates of asthma are climbing - but we should. As we did with breast cancer, we can marshall federal resources to study the causes of asthma as well as new treatments. Our funding of breast cancer research was popular with a certain constituency; in a like manner, parents may similarly support an effort to find the causes of asthma.

2. Launching a National Education Campaign on Asthma. A national education campaign would do some good here. Asthma is one disease in which educating parents about the symptoms and some of the instigators of attacks would alleviate some of the problem. In fact, New York City is already experimenting with ways to educate parents of asthmatic children by simply explaining to them that they need to get rid of rugs, stuffed animals, etc.

3. Grants to schools for medical equipment for asthma management that will be available for use in school nurses' offices. Arizona is starting such a program.

THE Children's Health FUND

MEMO TO: Jennifer Klein

FROM: Melissa Ziriakus

DATE: September 15, 1997

SUBJECT: Children's Health Fund press event

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Irwin Redlener and I have been in discussions to develop and provide you with a proposed outline for the New York City Asthma Initiative press conference on September 22 involving Ms. Hillary Clinton.

I've attached that for your review, and invite you to call if you have any questions.

HRC seen this before
1 TV crew
or couple of reporters

DS to Speaking Program, HRC to tour mobil unit

No Q & A

Find parent of child w/ asthma

What needs to be done to clinic

Review pieces of initiative

cc: Irwin Redlener, MD

Message

(1) Asthma - epidemic →
- all children
- high risk neighborhoods

HHS, EPA Accomp.
Other states doing anything

[Sanjay to talk to Irwin re Hunt's Point ~~Up~~ Rate]

(2) Connect to underserved children – ties into kid's health impl. & children's health fund work on

(3) → $314 M from Schering Plow -- Public - Partnership Partnership to Asthma

HRC to mention

The Children's Health Fund, 317 East 64th Street, New York NY 10021, Telephone (212) 535-9400, Fax (212) 535-7488

(4) Montefiore committed to building Children's Health System for South Bronx

→ Citywide program -- HRC child stress -- not just S. Bronx

Sanjay Gupta
12/10/97 07:33:03 PM

Record Type: Record

To: Brenda B. Costello/WHO/EOP

cc: Jennifer L. Klein/OPD/EOP
Subject: Final points

**FOOD SAFETY**

President Clinton asked for and received 43 million dollars in FY 98 budget to fund an early-warning system for food-borne illness, increased seafood inspections and expanded food-safety research.

Last year, President signed the Safe Drinking Water Act of 1996, which includes regulatory improvements to help states and water utility managers to prevent drinking-water contamination problems. Resources are provided for thr first time for drinking water infrastructure that will help hundreds of communities protect residents from harmful contaminants.

**done**

Sanjay Gupta
12/10/97 06:48:23 PM

Record Type: Record

To: Jennifer L. Klein/OPD/EOP

cc: Brenda B. Costello/WHO/EOP
Subject: Asthma

**ASTHMA**

The congressional report from HHS that I received states there are no recent bills directly addressed to asthma. I did find a few things that could be included in the briefing book for asthma. I'll try to be brief.

NHLBI (National Heart Lung and Blood Institute)
NIAID (National Institute of Allergy and Infectious Diseases)
NAEPP(National Asthma Education and Prevention Program)

1) Childhood Asthma Management Program -- examines and compares the long-term effects of asthma on lung growth and develpment
2) National Cooperative Inner City AsthmaStudy -- supports seven centers to design, implement, and evaluate a comprehensive intervention program to reduce recurrent asthma episodes among inner-city children
3)NAEPP has convened two expert panels to prepare guidelines for the diagnosis and management of asthma. The first in 1989 and the most recent in 5-97

AHCPR( Agency for Health Care Policy and Research)

1) Pediatric Asthma Patient Outcome Research Team (PORT II) -- will test the cost-effectiveness of the NHLBI (described above) and evaluate new educational and organizational approaches to deliver pediatric asthma care in managed settings

**CLEAN AIR**

Administrator Browner signed the new standards for smog and soot on July 16, 1997. These standards will prevent approx 350,000 cases of aggravated asthma. These standards are expected to prevent 15,000 premature deaths and 1 million cases of decreased lung function

In September 1996, Browner issued the National Agenda to protect Children's Health from Environmental threats. This agenda called on the EPA to address the special vulnerabilities of children - like susceptibilty to air pollution ans asthma.
In May, 1997, Browner created the Office of Children's Health Protection to

ensure implementation of the Agency's National Agenda

President Clinton signed the Executive Order on the Protection of Children from Environmental Health and Safety Risks (EO #13045) on April 21, 1997. This execuitve order stated that eachfederal agency must address environmental health threats to children in its regulations and programs. The executive order also created the Task Force on Environmental Health and Safety Risks which is chaired by Browner and Shalala.

**FOOD SAFETY**

Statement by the President Aug 3, 1996
Signed into law H.R. 1627 -- the "Food Quality Protection Act of 1996"

Replaces conflicting and outdated pesticide residue standards with a single, rigorous, health-based standards for all food. All pesticides will be required to meet the new standard. It will also provide for the swift approval of safe, new pesticide alternatives for farmers.

Most importantly, HR 1627 contains special new provisions to protect America's infants and children from pesticide risks.

Demonstrates how Congress and the Administration can work together to help both farmers and consumers.

**TOXIC WASTE**

Administration has strengthened and improved Superfund clean-ups. In first three years, 197 sites were cleaned up. This is more than in the previous 12 years of other administartion. This administration is cleaning sites three times more a year than were done before.

CONTACT:

THE CHILDREN'S HEALTH FUND
Melissa Ziriakus (212) 535-9400

SCHERING PLOUGH CORPORATION
William O'Donnell (973) 822-7476

COMMUNICATIONS STRATEGIES
Laurie Smith (973) 635-6669

**THE CHILDREN'S HEALTH FUND, SCHERING-PLOUGH CORPORATION, THE NEW YORK CITY COUNCIL, AND NYC DEPARTMENT OF HEALTH LAUNCH MAJOR INITIATIVE TO FIGHT ASTHMA**

BRONX, N.Y., December 11, 1997 — Tackling the urgent need to treat childhood asthma, The New York City Childhood Asthma Initiative today launched a nationwide effort to fight asthma in inner-city communities.

First Lady Hillary Rodham Clinton, speaking at a press conference at the South Bronx Children's Health Center, headed a list of dignitaries praising this innovative community-based effort that teams the public and private sectors to deliver asthma prevention and treatment services to neighborhoods with the greatest need. The multi-year, multimillion dollar program is a partnership of The Children's Health Fund (CHF), Schering-Plough Corporation, Montefiore Medical Center, and the New York City Council.

The New York City Childhood Asthma Initiative, brainchild of New York City Councilman Kenneth Fisher and CHF President Dr. Irwin Redlener, is designed to be a comprehensive treatment, prevention and education model to serve as a prototype for urban areas throughout the country. The New York City Council, under the leadership of Speaker Peter Vallone and Councilman Fisher, has provided $1.5 million in funding for the New York project.

-more-

**The Childhood Asthma Initiative/page 2**

Schering-Plough Corporation and Schering-Plough Foundation have provided funds estimated at more than $1 million to establish a primary care and asthma center in the South Bronx. Primary medical care and asthma speciality services will be provided by Montefiore Medical Center in the Bronx. Community education and outreach will be coordinated with other special asthma programs in New York City.

"Asthma is a serious illness, complicating many aspects of a child's life and becoming a chronic lifelong problem if left unmanaged," said Irwin Redlener, MD, president and co-founder of The Children's Health Fund. "Yet today, unlike just a few years ago, we know that there are ways to prevent the occurrence of asthma attacks and there are treatments available that can dramatically lessen its effects. Every day, we see the effect of asthma on children's lives, and we are excited to be able to implement a program that can have a significant, positive impact on the health of young children."

"What is sadly ironic about asthma is that so much emergency effort is spent to treat patients and we still lose too many children unnecessarily," said Richard W. Zahn, president of Schering Laboratories. "Given the many scientific advances in asthma treatment and prevention, it is unconscionable that this disease remains such as menacing problem. Children's lives can be saved and enhanced, if proper steps are taken."

An estimated 12- to 14 million Americans suffer from asthma; 5-6 million are children. These numbers are growing rapidly. Since 1980, there has been a 57 percent increase in asthma hospitalization rates for children less than 5 years old. Approximately 5,000 U.S. deaths are attributed to asthma annually. New York is particularly hard hit — it has the highest rate of asthma per capita in the nation. Asthma now ranks as the No. 1 health concern in many New York City schools, mainly elementary schools in poor areas and in minority communities.

-more-

**The Childhood Asthma Initiative/page 3**

"Asthma is at its worst in cities such as New York, where children are hospitalized for asthma at nearly twice the national rate," said Dr. Redlener. "Inner-city areas present a host of agents that can aggravate asthma, including outdoor allergens such as dust, mold and other indoor allergens including cockroach droppings and crowded conditions that can breed respiratory infections. Stress and tobacco smoke are also contributing factors."

"We have the opportunity to improve the quality of life for 120,000 children in New York. We can keep these children in schools, keep their parents at work and reduce health care costs by recognizing the tragic consequences of asthma and making it a public policy," said Fisher.

"The New York City Council is proud to be part of this partnership to tackle asthma in New York," said Speaker Vallone. "All children in this city deserve the opportunity to lead healthy, productive lives, and this initiative can help make that happen."

"As a nation, we must declare war on childhood asthma and allergies," said Zahn. "Today, The Children's Health Fund, Schering- Plough Corporation, Montefiore Medical Center and The New York City Council are dedicating ourselves to helping underprivileged children who suffer from these respiratory diseases."

The Children's Health Fund initiates and supports pediatric programs designed to meet the complex health care needs of medically underserved, homeless and indigent children. Now in its tenth year of operation, The Children's Health Fund was established by pediatrician Redlener and singer/composer Paul Simon.

-more-

In addition to the contribution to The New York City asthma initiative, a separate contribution from the Schering-Plough Foundation will fund the purchase of a dedicated CHF mobile medical unit for use in helping children in Newark and Elizabeth, N.J. and in the surrounding Union County area.

Schering-Plough Corporation is a research-based pharmaceutical and health care products company headquartered in Madison, N.J. Schering laboratories is the U.S. pharmaceutical business unit and Schering-Plough Foundation is the philanthropic arm of the parent company.

Today, company scientists continue to pursue new and more effective agents to prevent or block the effects of the body's allergic and immunological responses. In the disease management area, the company has developed comprehensive intervention programs to manage the coverage, quality and costs of disease treatments in asthma, rhinitis, angina, hepatitis and prostate cancer.

# # #

**FAX TRANSMITTAL COVER SHEET**

THE Children's Health FUND

| | |
|---|---|
| **To:** | Jennifer Klein |
| **Via Fax #:** | 202 456 2878 |
| **From:** | Dennis Johnson |
| **Date:** | 12/10 |

The number of pages in this fax (including this cover page): 5

If there is a problem with this fax transmission, please call (212) 535-9400 Ext. ____

Message:

Jennifer,

Attached is the correspondence about CHF / Dept. of Health agreement. Please call me if you need additional info.

Dennis

THE CITY OF NEW YORK
**DEPARTMENT OF HEALTH**
OFFICE OF THE COMMISSIONER

125 WORTH STREET
NEW YORK, NY 10013

BENJAMIN MOJICA, M.D., M.P.H.
ACTING COMMISSIONER
TEL (212) 788-5261
FAX (212) 964-0472

December 10, 1997

Kenneth K. Fisher
Council Member, 33rd District
16 Court Street - Room 1505
Brooklyn, NY 11241

Dear Council Member Fisher:

I have reviewed your memo of December 9, 1997 regarding the Asthma Initiative and the development of an agreement with the Children's Health Fund. I am pleased that this memo contains many of the suggestions we recently provided to you and Dr. Redlener. There are, however, a number of issues that require further clarification. I have noted below our comments on each of the items listed in your memo:

1. Any agreement for payment must be subject to an actual registered contract not just an agreed upon scope of service.

2. This is agreeable subject to legality and a review of the reasonableness of amount sought, as well as the factors cited in your memo. As stated several times in the past, we will be as flexible as is reasonable in this regard.

3. Agreed.

4. Agreed, but with the understanding that the partnership relationship extends to the planning and execution of all activities, including public relations activities surrounding the initiative.

5. Agreed.

6. The support is not limited to the Peninsula as the Hunts Point program extends over both zip codes 10474 and 10459. In addition, the DOH would be most comfortable if the support were to be provided out of the South Bronx Children's Health Center or, in the alternative, another location in the Hunts Point program area.

Kenneth K. Fisher
Council Member, 33rd District, cont.

7. Agreed.

8. Agreed. Guidelines and comments have already been provided.

9. We are unclear as to the intent of the phrase "work within" and do not feel it adds anything of substance to the discussion and may, in fact, limit collaboration.

10. Agreed.

I trust that you will find these comments helpful in reaching a quick resolution of outstanding issues. I have instructed my staff to contact Dr. Redlener to schedule a meeting as soon as possible to work on the contract. Finally, concerning the press conference, I have been advised that it is not appropriate to hold a press conference with Dr. Redlener announcing the citywide asthma initiative until a contract is in place. Therefore, I regret that I will not be attending the press conference.

Sincerely,

Benjamin Mojica, MD, MPH

KENNETH K. FISHER
COUNCIL MEMBER, 33RD DISTRICT
BROOKLYN

THE COUNCIL
THE CITY OF NEW YORK
CITY HALL
NEW YORK, NY 10007

CHAIR
LANDMARKS, PUBLIC SITING AND MARITIME USES

COMMITTEE ASSIGNMENTS:
ECONOMIC DEVELOPMENT
GOVERNMENT CONTRACTS
LAND USE
PARKS, RECREATION, CULTURAL AFFAIRS AND INTERNATIONAL INTERGROUP RELATIONS

TO: Benjamin Mojica, Acting Commissioner
NYC Department of Health

Irwin Redlener, MD
The Children's Health Fund

FROM: Kenneth K. Fisher

DATE: December 9, 1997

RE: Asthma Initiative

CC: Andrew Goodman, MD
James Capoziello
Karen Redlener
Dianne McLean, PhD
John Talmage
Mia Kozicharow

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I want to thank both of you for your efforts to this point. In the interest of moving forward I have memorialized the agreement as I understand it, with a further understanding that the following points will be incorporated in a formal contract.

1. The Department of Health agrees to provide The Children's Health Fund with $1.122 million dollars for the first year of the agreement, pending a mutually agreed upon scope of services.

2. The Department of Health agrees to make retroactive payments to The Children's Health Fund for expenses incurred since July 1, 1997 for the initiation, planning and development of the Initiative, assuming the expenses are relevant to the final agreement, within the scope of services, and The Department of Health has the authority to make such payments.

3. The Children's Health Fund agrees that the legal relationship between itself and The Department of Health will be that of purchaser/vendor.

4. The Department of Health agrees that the programmatic and public relationship between itself, The Children's Health Fund and The New York City Council will be that of partners.

5. The Children's Health Fund agrees to commit to a series of activities, including the development of a primary care and asthma center for children, a provider education program, and a mobile-based primary care and asthma program for homeless children.

6. The Children's Health Fund agrees to provide primary-care-based asthma education services, including an health educator, social worker, nurse asthma specialist and asthma intervention medical supplies for approximately 250 children, to the Hunts Point Peninsula community in partnership with existing Department of Health programs at that site. These education services may operate out of The Children's Health Fund's South Bronx Children's Health Center and/or a new primary care and asthma center.

7. The Department of Health agrees that The Children's Health Fund will operate a primary care and asthma center as part of the contract which may be implemented in another South Bronx community.

8. The Children's Health Fund agrees that the contract is predicated on a mutually agreed upon scope of services of sufficient detail which The Children's Health Fund will provide to The Department of Health. The Department of Health agrees to provide guidelines to and work collaboratively with The Children's Health Fund so that they can draft an appropriate scope of work.

9. The Department of Health agrees that all personnel paid for by The Children's Health Fund's portion of the funds will work within and report to The Children's Health Fund.

10. All parties agree that the remaining program will be finalized with The Department of Health within a reasonable period of time.

Again, I want to thank you for your cooperation and I look forward to participating in Thursday's press conference with you and putting a contract in place as soon as possible.

George [illegible]

Speech

# FAX COVER SHEET

Thursday, December 11, 1997 09:14:31 AM

To: Neera Tanden
Fax #: 12024562878

From:
Fax: 3 pages and a cover page.

# MEMORANDUM

**December 10, 1997**

**To: Hillary Clinton**

**From: Emily Jenkins, Tucson/Almaty HealthCare Coalition**

**Re: Synopsis of current issues regarding asthma from the perspectives of clinical treatment, research, and community efforts in education and prevention**

---

**Introduction**

Since our brief conversation in Almaty, I have been interviewing various experts regarding asthma as a health problem in the U.S., especially among children, and have assembled materials which I hope will be helpful to you in gaining an understanding of the problem and what has and needs to be done about it. For the sake of brevity, I will send a list of the specialists and background data under separate cover as an attachment to this document. Because of the in-migration of asthmatics to Tucson, the medical community and the University of Arizona College of Medicine have conducted long term research studies which have put Tucson in the forefront in clinical knowledge and expertise in research, especially in epidemiology, the analysis of the mechanisms of the disease, and the role of indoor air quality and environmental factors in the development of the disease.

**Asthma is a significant and growing health problem, despite advances in understanding and treating the disease**

For a quick description of the clinical aspects of the disease and the medications used to treat it, see pages 3-4 in *Tackling Asthma in Arizona.* This document also summarizes the key issues regarding the impact of the disease, since asthma is the chronic condition which causes the most hospital admissions for children and accounts for the most absenteeism from school. In the last 20 years, the death rate from asthma in the U.S. has increased 50 per cent. This increase has occurred in spite of advances in the clinical diagnosis and treatment of the disease and the reduction of particulates in the air in the environment. Much of the current research is aimed at these questions.

For children, there are some significant areas of concern:

- Children of lower socio-economic groups have more severe asthma than children of higher economic groups
- Black and Puerto Rican children have more asthma than children of other ethnic groups, including children of Mexican-American descent
- The development of the disease in children is not easily understood, and prevention and treatment issues are multi-faceted

**Guidelines for the diagnosis and treatment of asthma have been developed by the NIH and adopted by WHO for global application**

In April 1997, the National Heart, Lung and Blood Institute of the National Institutes for Health issued updated **Clinical Practice Guidelines for the Diagnosis and Management of Asthma** (copy sent under separate cover). These NIH guidelines have been modified and adopted by WHO (*Global Initiative for Asthma* sent under separate cover). Research in Tucson and other places has established that adherence to the guidelines results in improved outcomes for patients. These guidelines incorporate the new drugs and therapies and also the diagnostic tools available to physicians and patients to monitor the disease. **The barriers to the successful implementation of the guidelines appears to be the need to educate physicians who treat children, including pediatricians, family practice specialists, and physicians in urgent care and emergency departments.** Nurses and paramedic personnel also need to be included. A model project is the **Tucson Alliance for Pediatric Asthma Care,** which provides educational programs to physicians, nurses, school nurses, daycare providers, athletic coaches and other persons who regularly have custodial relationships with children. The programs include families and trains health care volunteers and staff as patient and family educators.

**The role of the patients and the families are critical in this process.** Even very young children can learn to use a peak flow meter to monitor their airway status, and parents must monitor the use of the medication and be certain that there is continuous treatment of the disease. Parents also need to create an environment in the home which reduces triggers for the disease, such as cigarette smoke, dust mites, cockroach and rodent urine, dog and cat dander, formaldehyde-impregnated carpets and furnishings, and other regional allergens such as mold and mildew.

**This need for parents to be proactive may be one of the reasons why children of lower socio-economic status have more asthma and more severe disease.** Parents of children at risk for asthma or with asthma must have access to a quality health system and seek out care early on, not only for asthma but also for respiratory infections that can lead to the development of the asthma. **Seeking medical care only when the child is having a severe attack is not effective in preventing or managing the disease. The ability to change the home environment may also be beyond the capability of these parents.** The Inner City Asthma Project currently being funded by NIH will study the impact of effective treatment and home environmental and patient/family education programs on populations in several regions of the country, including Tucson. This five year program should provide the data needed to support changes in services and environmental conditions by physicians, managed care plans, state and local health agencies and providers, and other organizations, such as schools, day care providers and housing authorities. Managed care plans and Medicaid providers must be convinced of the need for early intervention in diagnosis and treatment of children with asthma, including patient and family education, allergen testing, and easy access to health providers for these children.

**What needs to be done to prevent the development of asthma and to limit its impact on the health of children?**

1. Community wide programs such as the Tucson Alliance for Pediatric Asthma need to be conducted to implement what is already known and established in the areas of clinical diagnosis and treatment, education for patients, families, and care providers, and control of indoor air quality in homes, schools, day care centers, and other places where children spend their time.
2. Managed care plans and other insurance programs such as Medicaid need to provide accessible health care services to asthmatic children or children at risk for asthma, including educational programs and case management services to support the families to assure compliance.
3. Public attention needs to be directed to this problem, with special attention to primary prevention efforts, which include elimination of smoking during pregnancy, protection of infants and small children from indoor air pollutants, and early treatment of respiratory infections which can lead to the development of the disease.
4. Research needs to be continued in the areas of the development and treatment of the disease, the regional (geographic) variances in environmental factors, genetic factors, and variances in incidence in socio-economic groups.

**Asthma in the Elderly Population**

**The longer people live, the more likely it is that they will develop asthma**, especially if they have a history of smoking or respiratory disease or infections. **As the population ages, the incidence of asthma will increase**. Research indicates that children may appear to "outgrow" their asthma, but actually it smolders and often reappears in later life. When asthma occurs along with other diseases of the elderly, such as congestive heart failure, it can be difficult to diagnose and treat. An aging population will require diagnostic and treatment services, and environmental conditions in nursing homes must be addressed.

**Gaining a comprehensive understanding of the problem of asthma and what needs to be done**

If you would like to increase your understanding of the issues surrounding asthma and what is known and can be implemented to prevent and limit the impact of the disease, I invite you to Tucson. I will organize a program which will include:

1. discussions with national and international experts in clinical and research areas
2. discussions with physicians regarding patient care issues
3. a briefing on the Inner City Asthma Project, including a tour of the El Rio Community Health Center, which will be the research site
4. briefing on the Tucson Alliance for Asthma Care which operates under the auspices of the Tucson chapter of the American Lung Association
5. meeting with families and children regarding their experiences in learning about and monitoring their asthma and the impact which it has on their lives.
6. discussion of the present and future role of managed care plans in providing coverage and prevention programs (Arizona has a managed care alternative Medicaid program)

*TUCSON/ALMATY HEALTHCARE COALITION*

*TEL: 520-324-1784*
*FAX: 520-795-5689*

*Tucson Medical Center, Arizona Building, 2nd floor, 5301 East Grant Road, Tucson, Arizona 85712*

# FAX COVER SHEET:

Brenda

**DATE:** 12/9/97 **TOTAL PGS:**

**TO:** Nera Tanden Tel:
Fax:

**FROM:** Emily Jenkins Tel:
Almaty Project Fax: 795-5689

**RE:** 202 456 2878

Good summary of issues - Arizona + U.S.

# Tackling Asthma in Arizona

## A Report by the Arizona Asthma Coalition

August 1997

## ARIZONA ASTHMA COALITION

The Arizona Asthma Coalition, a prevention partnership, was formed in 1996 with five objectives.

### OBJECTIVES

- Collaborate and build partnerships to improve asthma management
- Increase awareness of asthma management
- Share data and information
- Evaluate the effectiveness of interventions
- Advocate for public health priorities and activities

It is our hope that appropriate legislative, administrative and medical bodies will act upon the recommendations contained in this report.

The Coalition membership includes the following groups:

Academy of Family Physicians, Arizona Chapter
Academy of Pediatrics, Arizona Chapter
ADHS/Arizona Center for Minority Health
ADHS/Health Planning, Evaluation & Statistics
ADHS/Community & Family Health
ADHS/Women & Children's Health
ADHS/Public Health Policy & Practice
ADHS/Chronic Disease Prevention
ADHS/Chronic Disease Epidemiology
Arizona Disease Control Research Commission
Aetna US Healthcare
AHCCCS
American Lung Association of Arizona
Arizona Asthma and Allergy Institute
Arizona Physicians, Inc.
Arizona HMO Association
Arizona Public Health Association
Asthma Information Resources
BlueCross BlueShield
Cathy Graeff, Inc.
CIGNA Healthcare
Coconino County Health Department
Faculty from the U of A, Health Sciences Center
Glaxo Wellcome, Inc.
Health Services Advisory Group
Health Partners Health Plan
Humana Inc.
Intel Corporation
Intergroup of Arizona, Inc.
Kid Radio KHITS
Merck and Company, Inc.
Maricopa County Department of Health
Maricopa Managed Care Systems
Mercy Care Plan
Mohave County Department of Health
Murphy Elementary, School District 21
PCS Health Systems
Phoenix Children's Hospital
Phoenix Pediatrics
Samaritan Prime Care Network
Scottsdale Memorial Home Health Care
Scottsdale Memorial Hospital North
Signature Homecare
St. Joseph's Children's Hospital
University of AZ College of Pharmacy
Your Family Physicians

## WHAT IS ASTHMA?

Asthma, once thought of as a "simple" hypersensitive reaction, is now known to be a complex condition with a spectrum of causes and contributing factors, with airway inflammation as its central attribute.

Asthma is a reversible obstructive lung disease, caused by an increased reaction of the airways to various stimuli. It is a chronic condition with acute exacerbations. Asthma can be a life-threatening disease if not properly managed.

Asthmatics have bronchial tubes that are virtually continuously inflamed and hyperactive, sent into suffocating spasms by a broad range of provocations that may vary from one individual to another. Some of the substances and circumstances that may trigger attacks are: smoke, airborne molds, pollens, dust, animal dander, exercise, cold air, many household and industrial products, air pollutants, scents, and simple stress. An episode finds the victim gasping for breath as the airways become constricted, the passages inflamed and clogged with thick, sticky secretions. The narrowed airway is responsible for the difficulty in breathing with the familiar "wheeze."

## WHAT IS THE TREATMENT?

Those who suffer from asthma must typically take a variety of medications, usually on a regular basis. They include bronchodilators, corticosteroids, and other reducers of inflammation. With the recent recognition of the major role played by continuing inflammation, regular use of inhaled steroids is increasingly advised. Complying with these often complex treatment regimens can prove particularly difficult for children.

Two classes of medications are used to treat asthma--bronchodilators and anti-inflammatory agents. Bronchodilators act principally to dilate the airways by relaxing bronchial muscle. They include beta-adrenergic agonists, methylxanthines, and anticholinergics.

Anti-inflammatory agents interrupt the development of bronchial inflammation and have a prophylactic or preventive action. They may also modulate or terminate ongoing inflammatory reactions in the airways. These agents include corticosteroids, cromolyn sodium or cromolyn-like compounds, and other anti-inflammatory compounds.

## ASTHMA PREVALENCE IN ARIZONA

- According to the Arizona Department of Health Services, an estimated 210,000 asthmatics reside in Arizona.

- Hospital discharge rates for pediatric asthma in Arizona are highest among African-Americans (see graph #1), approximately 4 times that of Hispanics and Whites.

- Hospital discharge rates for asthma in 1995 were highest in Yuma County followed by Maricopa County (see graph #2).

- The asthma death rate in Arizona in 1995 was 2.8 per 100,000 while the death rate in the United States was 2.1 (see graph #3).

- According to the Arizona Department of Health Services, Maricopa County had the third highest death rate from asthma compared with other counties in the United States.

- Asthma hospitalizations in 1995 were highest in the last quarter of the year, the time of year with the highest levels of airborne particulate matter in Arizona (see graph #4).

## ASTHMA PREVALENCE NATIONWIDE

- Asthma affects 14 to 15 million persons, including 4.8 million children under the age of 18.

- Between 1982 and 1992, the prevalence rate--the rate per thousand persons--of pediatric asthma rose from 40.1 to 63.4, an increase of 58 percent.

- Some of this increase in prevalence may be due to "diagnostic exchange," the tendency for physicians to label patients with asthma instead of an alternative diagnosis, but this only accounts for part of the increase in prevalence.

- The number of deaths attributed to asthma has increased by 98.9 percent since 1979, from 2,598 in 1979 to 5,167 in 1993.

- For persons under age 25, the annual age specific asthma death rate increased 118% between 1980-1993.

- Annual hospitalization rates among persons age 25 and under increased 28% from 1980- 1993.

## ASTHMA IN CHILDREN

- Asthma is the leading serious chronic illness among children. Most children have mild problems, and their illness can be controlled by treatment at home or in the doctor's office. For some children the illness becomes a formidable problem causing many visits to the hospital emergency room and multiple hospitalizations.

- Asthma accounts for 10 million lost school days annually. It is the leading cause of school absenteeism attributed to chronic conditions.

- Asthma is the third-ranking cause of hospitalization among children under the age of 15; it is the first-ranking cause among chronic conditions.

- Secondhand smoke can cause serious harm to children. An estimated 200,000 to one million asthmatic children have their condition worsened by exposure to secondhand smoke.

- Children are more vulnerable than adults to air pollution because they breathe more rapidly and inhale more pollutants per ratio of body weight than adults.

- Only about a quarter of the children with asthma outgrow the condition; for the rest, the condition is a lifelong ordeal. The condition persists in 85 percent of women and in 72 percent of men who had the disease as children.

## COSTS

- Hospital charges for treating children with asthma amounted to $12 million in Arizona in 1995. Addition uncounted costs include emergency room visits, physician costs, lost work days, and missed school.

The annual direct health care cost of asthma nationwide is approximately $9.8 billion; indirect costs (e.g., lost work days) add another $2.8 billion, for a total of $12.6 billion. The largest single direct cost may be emergency room use estimated to account for 43% of the direct costs. Asthma also accounts for an estimated 10.1 million missed days from school and 200,000 hospitalizations per year in children less than 18.

## WHO GETS ASTHMA?

- Recent studies suggest that children of smokers are twice as likely to develop asthma as children of nonsmokers.

- Women who smoke during pregnancy have babies with abnormally narrowed airways that predispose them to asthma.

- Although African-Americans represent approximately 12 percent of the U.S. population, they account for 21 percent of deaths due to asthma. The reason for this discrepancy is unknown.

- In 1982, the prevalence rate of asthma among African-Americans was 13.3 percent higher than the rate among whites; in 1992, the rates for both races were up--but the rate among blacks was 15.4 percent higher than that for whites.

## COALITION RECOMMENDATIONS

Based on the asthma prevalence and mortality compared to other states, the Arizona Asthma Coalition recommends:

- Work in conjunction with managed care organizations to implement the guidelines from the National Institutes of Health on diagnosing and managing asthma. Because over 80% of Arizonans covered by health insurance receive care through HMO's, these systems provide the most effective route to implement "best practices." Some HMO's in Arizona are already providing leadership in asthma care.

- Train providers such as physicians, nurse practitioners and nurses in up-to-date asthma prevention and treatment protocols. Establish a certification process for primary caregivers, especially in the area of pediatric asthma management.

- Provide self-care education and resources for patients and families with asthmatic children.

- Target improved asthma management services to communities with disproportionally high rates of hospitalization from asthma.

- Improve funding and equipment for school-based health care providers and ensure that each school has a full-time certified asthma care provider. Asthma is the number one cause of school absences. School-based providers can play a vital role in treating and educating children with asthma and in preventing emergency room visits from uncontrolled asthma episodes.

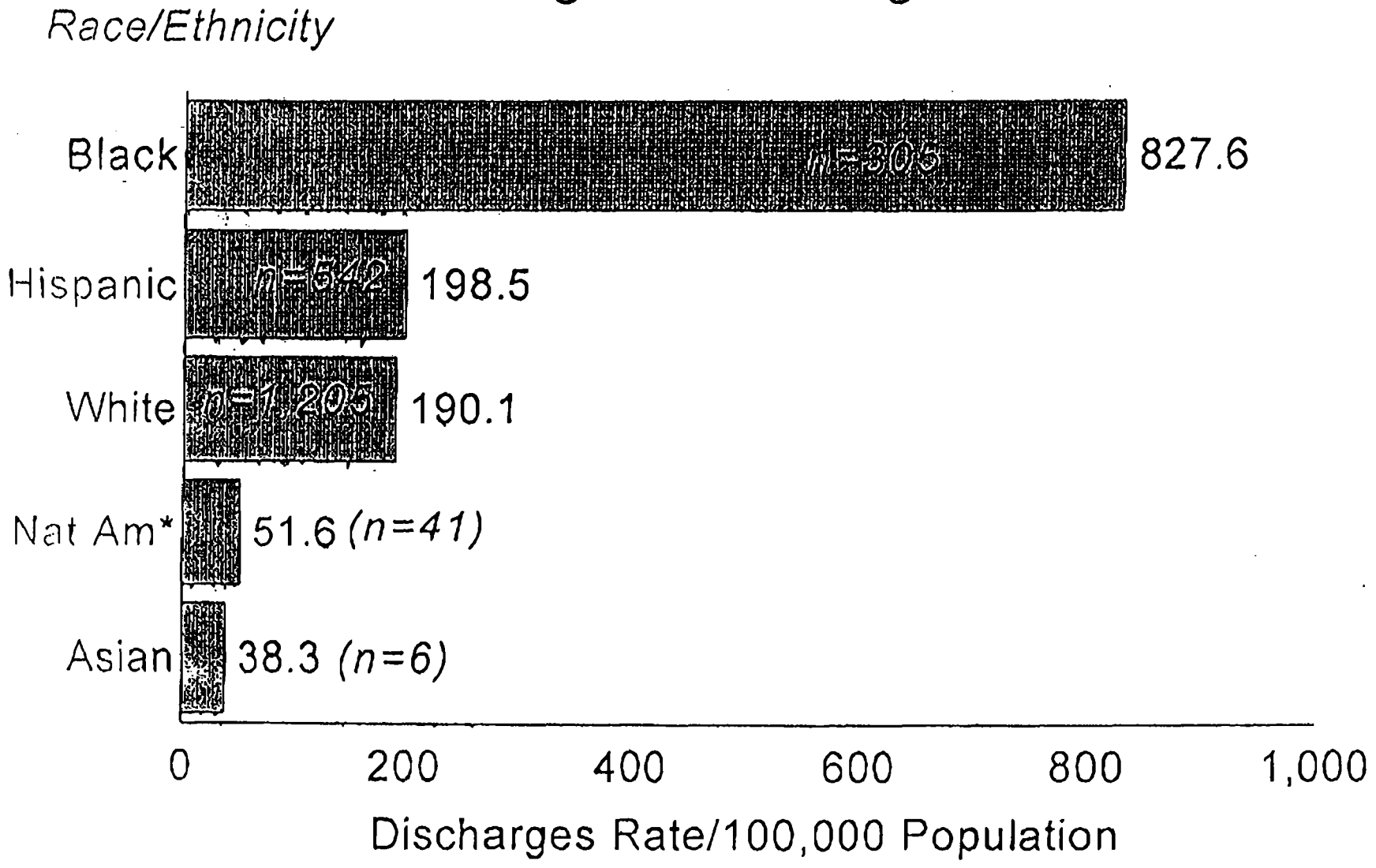
- Implement clean indoor air laws around the state, including a ban on smoking in the workplace. Research shows a link between passive smoking and increased exacerbations of asthma.

- Implement control measures to reduce airborne particulates in order to help us achieve the federal Environmental Protection Administration (EPA) health standard for particulate pollution. Research shows a link between poor outdoor air quality and higher morbidity rates. The relationship is most apparent with particulate pollution. By December 1997 Arizona must submit a plan to reduce particulates to EPA.

# 1995 Arizona Asthma Hospital Discharges*
## *By Race/Ethnicity-Specific Rates*
## *Among Children Age 2-20*

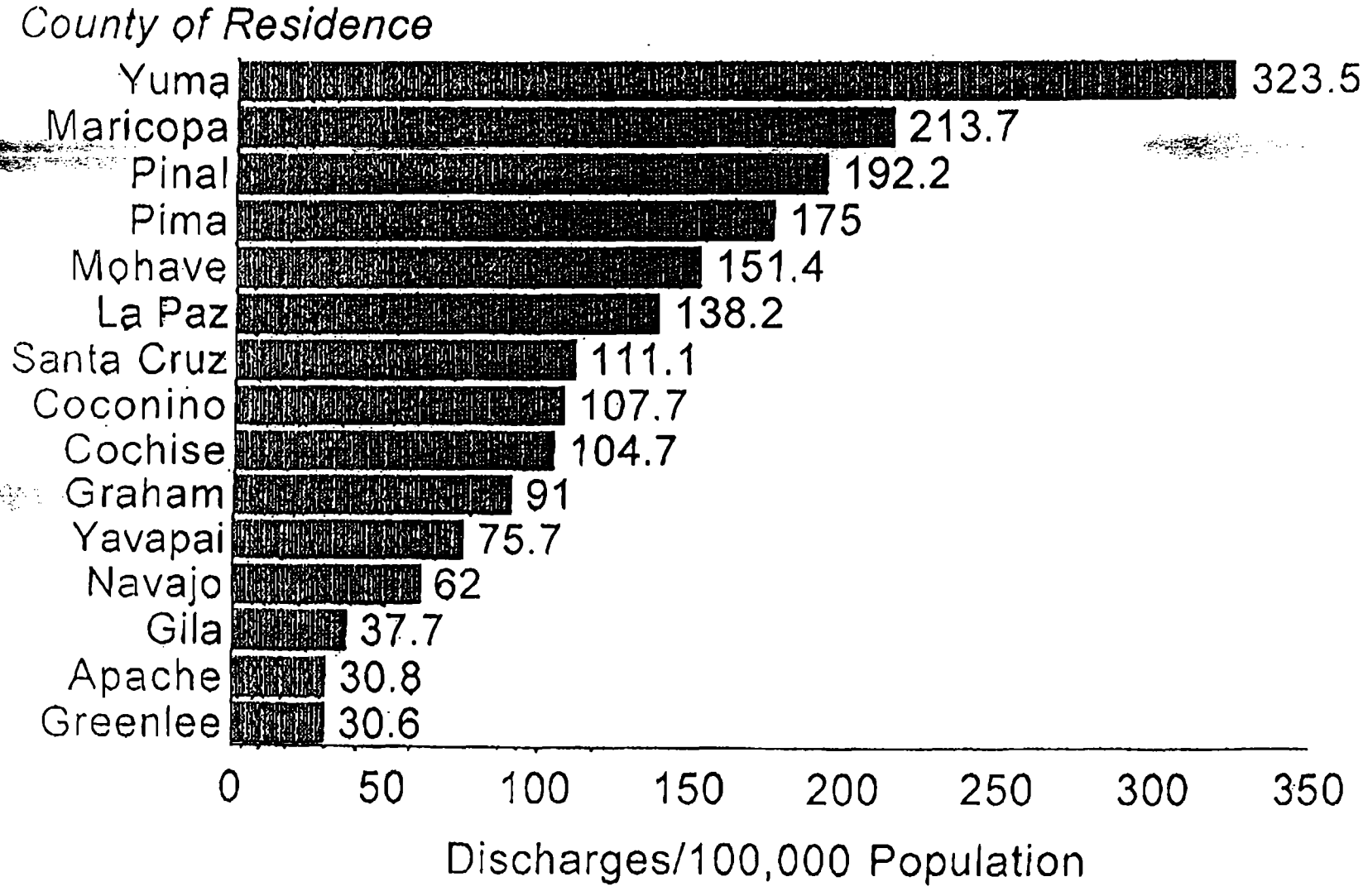






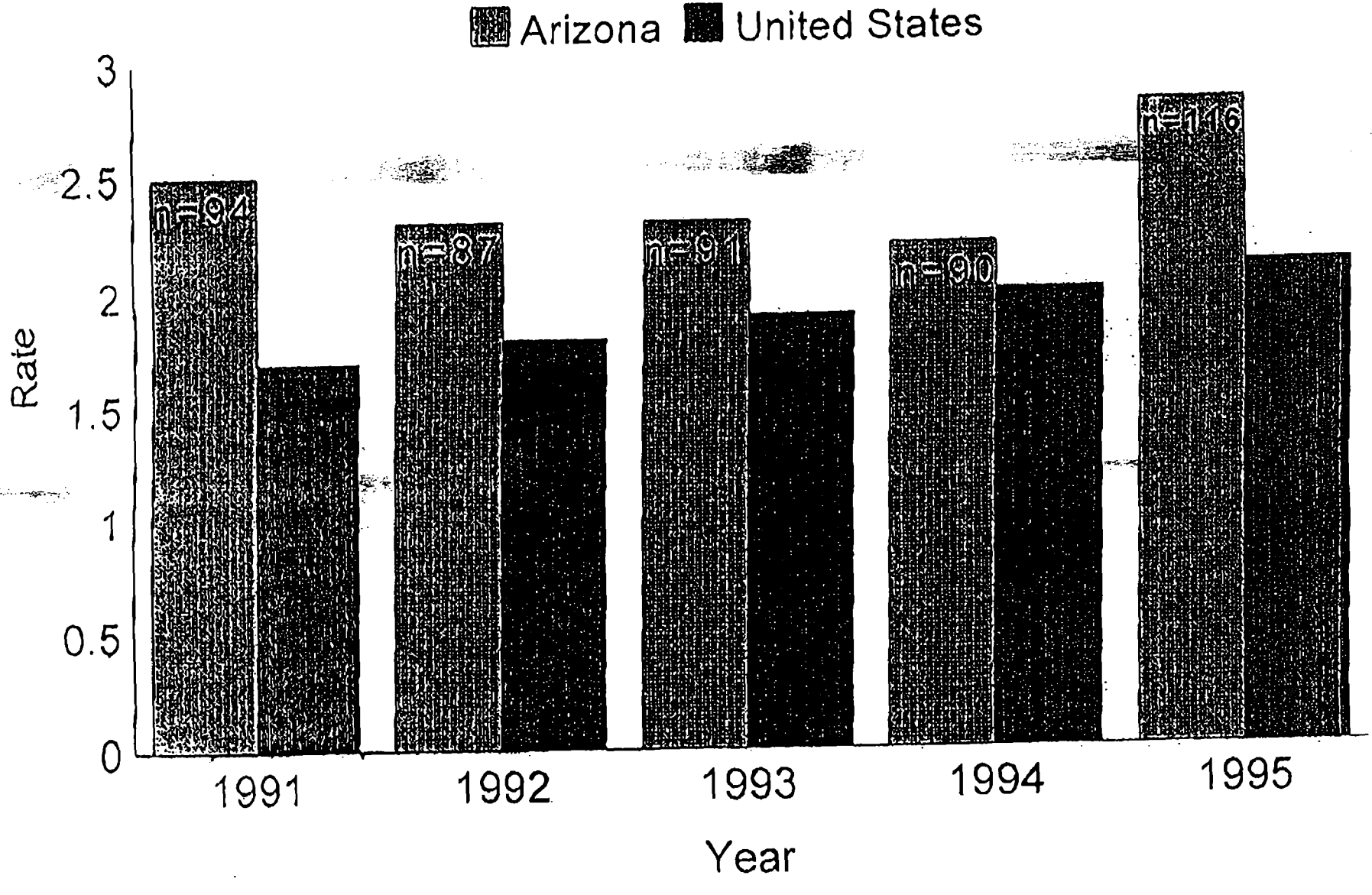

*Arizona hospital discharges from non-federal facilities (Does not include IHS facilities)
Note: Rate based on Arizona 1990 Census Population

# 1995 Asthma Hospital Discharge Rate
## *By County For Children Age 2-20*




Arizona hospital discharges from non-federal facilities (Does not include IHS facilities)
ote: Rate based on ADES 1995 Population Projections

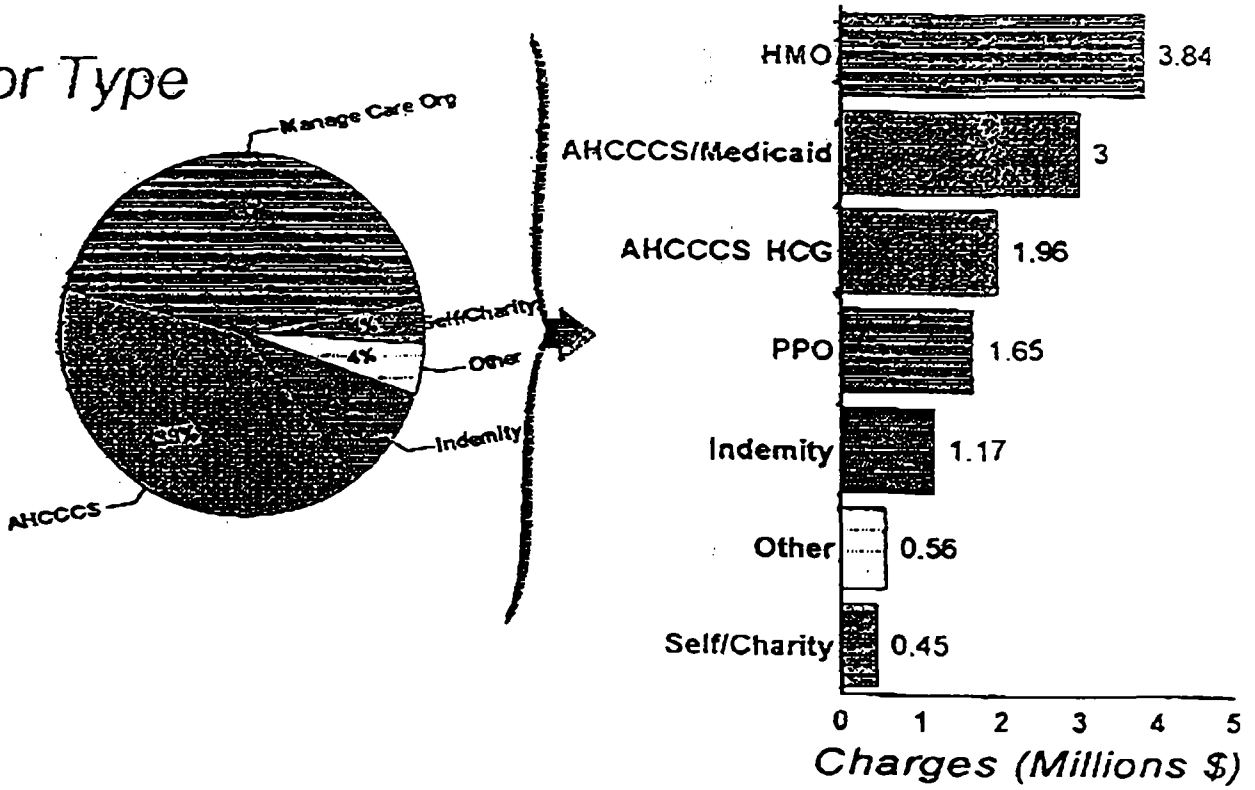
# Asthma Death Rate*
## Arizona and United States, 1991-1995




*Number of Deaths per 100,000 population
Source: Arizona Department of Health Services; Office of Planning, Evaluation, and Statistics

# Hospital Asthma Charges Among Children in Arizona During 1995 ($12,614,344)*

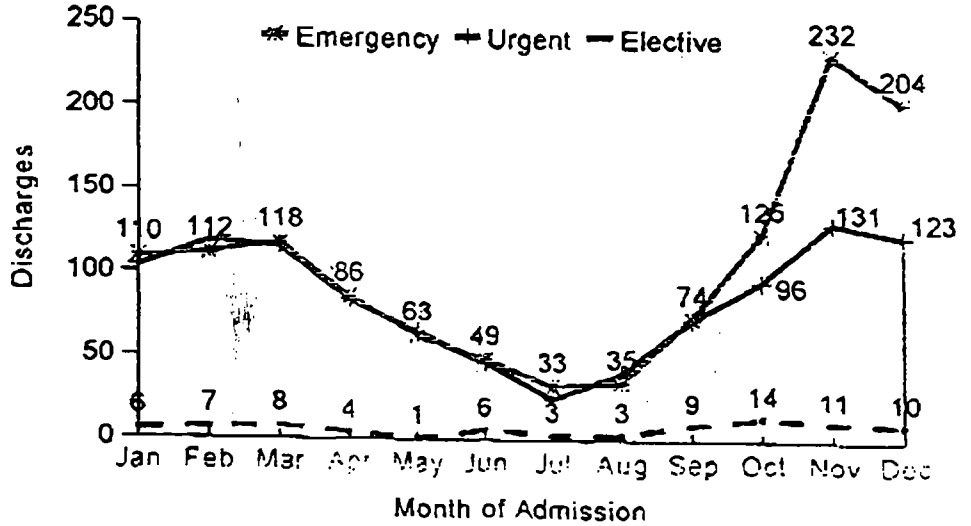
## Payor Type




*Other includes CHAMPUS, Child Rehab, Work Comp, IHS, Foreign Nation*
**All discharges from non-federal facilities among children age 2-20*

4

## Asthma Hospital Discharges*
### Among Children Age 2-20 During 1995 (2,346 Discharges)




*Discharges From All Non-federal facilities

**MEMORANDUM TO** **JENNIFER KLEIN**

**FROM** **SANJAY GUPTA**

**RE** **PEDIATRIC ASTHMA**

# ASTHMA IN CHILDREN

## KEY FACTS

### What is asthma?

- Asthma is a chronic inflammatory disorder of the airways. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes, or "asthma attacks", are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment.

- Asthma can vary in severity and is categorized as either: mild intermittent, mild persistent, moderate persistent or severe persistent.

- Asthma often begins in childhood and can start as early as the first year of life: 70% of all people with asthma developed asthma before age seven.

- Asthma is frequently found in association with what is referred to as "atopy", the susceptibility to produce antibodies toward common allergens such as animals, cockroaches, house-dust mites, indoor molds and outdoor allergens.

- Other factors that can precipitate or **trigger** asthma attacks include: tobacco smoke, indoor/outdoor pollution, viral respiratory infections, trauma and other stressors, exercise, drugs, emotions, cold air, aspirin and sulfite sensitivity.

**Who has asthma?**

- As of 1994, approximately 4.8 million children under the age of 18 have asthma, according to the National Institute for Allergy and Infectious Diseases, for a prevalence rate of 4.3%. Nationally, asthma rates are highest in New York, Chicago, Fresno, California and Maricopa County, Arizona. Asthma prevalence and mortality rates are continuing to rise nationwide.

- In 1994, in high risk areas of New York City the asthma prevalence rate for children reached between 8.6% and 14%. In 1996, it reached 25% for the population of homeless children cared for by The Children's Health Fund.

- As of 1993, New York City children were hospitalized for asthma at more than four times the national rate and the hospitalization rate is continuing to rise. Within New York City, African Americans and Latinos have three to five-and-and a- half times the hospitalization rates of whites. Among New York City children 14 and younger, those living in a zip code in the lowest 20th percentile of median income had four times the hospitalization rate of those living in the highest 20th percentile of median income. Areas in New York City with highest asthma hospitalization rates include the South Bronx, Upper Manhattan , Central and North Brooklyn.

- The number of children hospitalized for asthma nationwide has increased fivefold over the past 20 years. In 1993, asthma accounted for nearly 200,000 hospitalizations among people less than 25 years old.

- Hospitalization rates for children less than five years old have increased by 57% since 1980.

- Compared with white children, African American children are four to six times more likely to die from asthma and three times more likely to be hospitalized for asthma.

- Poor children with asthma reported 40% fewer physician visits, yet were 40% more likely to be hospitalized than children with more economic resources.

**What are the consequences of asthma for children?**

- Nationwide, asthma is associated with the loss of 28 million activity days annually and 2.2 million pediatrician visits. It is the leading cause of school absenteeism. It has been estimated that among children 5-17 years old, asthma accounted for approximately 10 million missed school days, at a cost of $726.1 million in caretaker's time lost from work.

- Asthma can be fatal. Over 3,800 children and young adults under 25 died from asthma nationwide during the period of 1980-1993. In 1993 alone, 342 children and young adults under 25 died from asthma.

**What are the costs of asthma?**

- In 1993, the total direct and indirect annual costs of asthma were estimated to be over $6.2 billion in 1990 dollars, not including the economic impact of this disease on affected patients and families.

- Non-monetary costs for children with asthma include decreased

quality of life, mental distress for patients and families, social labeling associated with a chronic disease and complications from medication use.

CLASSIFICATION

# AIR FORCE ONE FAX

To: Jen Klein 62828

~~FROM~~: ~~David Shapley~~

From ~~TO~~: Michael O'Mara 456-5709

REMARKS: Michael - Pls. send this 0/6 to Jen + Sanjay:

Thx. D

AF1 FAX NUMBER :

DATE-TIME GROUP :

TOTAL PAGES :
(TOTAL INCLUDES COVER)

CLASSIFICATION

DRAFT 12/9/97

# FIRST LADY HILLARY RODHAM CLINTON

# STATEMENT FOR NEW YORK CITY CHILDREN'S ASTHMA INITIATIVE

# SOUTH BRONX CHILDREN'S HEALTH CENTER

# DECEMBER 11, 1997

Acknowledgments. From advance

Today we take another step in our comprehensive effort to protect the health of America's youth -- a step that will meet head on the most common chronic medical problem children face today: asthma. And like all important steps, it is one we are taking together: doctors, nurses, health care providers, community leaders, government, citizens, and parents.

Asthma affects nearly 5 million American children. Over the past decade, it has led to more than 4000 deaths. Worse, these numbers are on the rise. In the last 20 years, the number of children hospitalized for asthma has increased five-fold; the number of deaths has more than doubled.

We also know asthma hits hardest the children of our inner cities. New York City children, for example, are hospitalized at four times the national rate. Moreover, the hardest hit of the hardest hit are minorities -- African Americans and Latinos.

Here in New York, the asthma rates for African American and Latino children are three to five times higher than rates for other populations. An African American child is four to six times more likely to die from asthma than a white child.

Behind these statistics, there are human stories. Children who cannot step outside the front door without a pocketful of inhalers. Children who cannot walk a block or ride a bike without grasping for air. Children who miss out on education, friendship, and community because of their condition. Asthma is the leading cause of school absenteeism. Last year, it was the cause of more than 10 million missed school days. To a parent, there are few things more frightening than seeing the look [illegible] on your child's face as he or she is struck by asthma. To

These resources will go toward providing health care coverage for children who are currently uninsured. Up to 10 percent of these funds can be used for on-the-ground services -- like those we see here today.

Earlier this year, the President announced a plan to see to it that parents and doctors know exactly what and how much medicine to give children. Right now, the vast majority of medications -- including asthma drugs -- are not tested for kids. The President's Pediatric Labeling Initiative will change all that. No parent should have to guess how much medicine to give a sick child.

During the course of his administration, my husband has taken a series of other important steps to safeguard the health of our children: from protecting and defending Medicaid...to signing cutting-edge legislation like the Family and Medical Leave and Kennedy-Kassebaum Acts...to shielding our young people from tobacco and drugs...to seeing to it that our children get the immunizations they need.

He has also made a special effort to see to it that the air our children breathe, the water they drink, and the food they eat are safe. The President issued [redacted] public health standards for smog and soot that will prevent 350,000 cases of aggravated asthma. He has cleaned up a record number of toxic waste sites and expanded community right to know laws so that families know exactly what substances are being released into the world around them. Under this administration, we have strengthened and revolutionized food safety laws for meat, seafood, and poultry for the first time in a generation -- and we have toughened regulations to keep harmful pesticides off our children's food.

All these efforts work toward a single dream: Better health and safer lives for our children. With today's initiative -- and with your work and commitment -- we are one step closer toward making that dream a reality.

Thank you.

DAVID SHIPLEY [redacted]
12/09/97 01:51:38 PM

Record Type: Record

To: Jennifer L. Klein/OPD/EOP, Sanjay Gupta/WHO/EOP, OMARY_M @ A1 @ CD @ LNGTWY

cc:
Subject: edit of asthma speech. as you can see, there are some questions. thanks, d

**DRAFT 12/9/97**

**FIRST LADY HILLARY RODHAM CLINTON**
**STATEMENT FOR NEW YORK CITY CHILDREN'S ASTHMA INITIATIVE**
**SOUTH BRONX CHILDREN'S HEALTH CENTER**
**DECEMBER 11, 1997**

Acknowledgments. From advance

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We also know asthma hits hardest the children of our inner cities. New York City children, for example, are hospitalized at four times the national rate. Moreover, the hardest hit of the hardest hit are minorities -- African Americans and Latinos. Here in New York, the asthma rates for African American and Latino children are three to five times higher than rates for other populations. An African American child is four to six times more likely to die from asthma than a white child.

Behind these statistics, there are human stories. Children who cannot step outside the front door without a pocketful of inhalers. Children who cannot walk a block or ride a bike without grasping for air. Children who miss out on education, friendship, and community because of their condition. Asthma is the leading cause of school absenteeism. Last year, it was the cause of more than 10 million missed school days. To a parent, there are few things more frightening than seeing the look of confusion and then fear on your child's face as he or she is struck by asthma. To a child, I cannot imagine anything more terrifying than not being able to breathe -- no matter how hard you try.

That is why I am so gratified by the action you are taking today. The Children's Health Fund, the Montefiore [Monta-fee-or] Medical Center, and [*what level of govt? Are we involved?*] have come together to create an innovative public-private partnership to lower the rates of childhood asthma. This initiative will increase public awareness of pediatric asthma through programs, models and policies [*can we be more specific about this? Will teach parents to take their kids for checkups? Get away from cockroaches? What?*]. Mobile medical units and primary care centers will provide treatment to homeless children and those at particular risk. *[need one more specific here. What does it do for real people?]* If there is any disease that illustrates that an ounce of prevention is worth a pound of intensive care, asthma is it.

children, for parents, child care docs providers, teachers and mgmt care prof.

This is part of the President's *[are we involved? Is there govt support? If so, say above wrt people coming in pub-priv partnership. If not, trans should be, "what you are doing here fits with the president's efforts to build a...* ] overall commitment to building a strong foundation for the health of all our children. This summer, the President signed into law a balanced budget that will help extend health insurance to up to 5 million children.

During the course of his administration, my husband has taken a series of important steps to safeguard the health of our children: from protecting and defending Medicaid...to signing cutting-edge legislation like the Family and Medical Leave and Kennedy-Kassebaum Acts...to shielding our young people from tobacco and drugs...to seeing to it that our children get the immunizations they need.

He has made a special effort to see to it that the air our children breathe, the water they drink, and the food they eat are safe. The President issued tough new public health standards for smog and soot that will prevent 350,000 cases of aggravated asthma. He has cleaned up a record number of toxic waste sites and expanded community right to know laws so that families know exactly what substances are being released into the world around them. Under this administration, we have strengthened and revolutionized food safety laws for meat, seafood, and poultry for the first time in a generation -- and we have toughened regulations to keep harmful pesticides off our children's food.

All these efforts work toward a single dream: Better health for our children. With today's initiative -- and with your help and commitment -- we are one step closer toward making that dream a reality.

Thank you.

THE Children's Health FUND

**FAX TRANSMITTAL**
**COVER SHEET**

To: Jennifer Klein
Via Fax #: (202) 456-2878
From: Melissa Ziriakus
Date: September 16, 1997

The number of pages in this fax (including this cover page): 6
If there is a problem with this fax transmission, please call (212) 535-9400

Proposed outline for December 11, 1997 Children's Health Fund press event. I look forward to speaking with you about details and can be reached at (212) 535-9400, ext. 280.

THE Children's Health FUND

**Memo to:** Jennifer Klein

**From:** Melissa Ziriakus

**Date:** December 2, 1997

**Subject:** Children's Health Fund press event

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Irwin Redlener and I have been in discussions to develop and provide you with a proposed outline for the New York City Asthma Initiative press conference on December 11 at 11:00 AM involving Ms. Hillary Clinton.

I've attached that for your review, and invite you to call if you have any questions.

Separately, I also sent to Sanjay Gupta, via FedEx today for tomorrow morning delivery, a copy of the childhood Asthma Briefing Book, along with some other program orientation pieces.

M. Ziriakus

cc: Irwin Redlener, MD

120297 15:20

DRAFT DRAFT DRAFT DRAFT

## The Proposed Plan
## to Announce
## The New York City Childhood Asthma Initiative

WHAT: A press conference for **The Children's Health Fund** to announce a major public health initiative, **The New York City Childhood Asthma Initiative,** and plans to develop a **primary care and asthma center.** This is an opportunity to unveil the program components, to talk with principals involved, and dignitaries who support the initiative as an effort to fight against the epidemic of asthma. This comprehensive plan is designed to be a model for programs that can be executed throughout the United States.

WHO: An exceptional coalition of:

- **FEDERAL INTERESTS**: The White House, Ms. Hillary Rodham Clinton;
- **LOCAL GOVERNMENT**: The City Council of New York, led by Councilman Kenneth Fisher;
- **PUBLIC HEALTH ADMINISTRATION**: the New York City Department of Health, represented by Benjamin Mojica, Acting Commissioner;
- **THE CHILDREN'S HEALTH FUND and MONTEFIORE MEDICAL CENTER**: spearheaded by Irwin Redlener, MD;
- **PRIVATE SECTOR:** Schering Laboratories, represented by Richard W. Zahn, president.

WHAT: The New York City Childhood Asthma Initiative addresses the epidemic proportions of asthma in New York City, where incidence of the disease is among the highest in the nation. The press conference is to advise the community, via the press, of the diverse efforts that the Initiative will introduce, and to introduce the plan as a national model.

WHEN: Thursday, December 11, 1997
11:00 am
Time frame: approximately 20 minutes to one-half hour;

WHERE: South Bronx Children's Health Center
911 Longwood Avenue
The Bronx, New York.

OTHER:

Speakers
- Irwin Redlener, MD, President, The Children's Health Fund; Vice President for the Children's Medical Center, Montefiore Medical Center;
- Kenneth Fisher, Councilman, Borough of Brooklyn;
- Benjamin Mojica, MD, Acting Commissioner, NYC Department of Health;
- Richard W. Zahn, President, Schering Laboratories;
- Hillary Rodham Clinton, Esq., First Lady of the United States.

Other invited, nonspeaking guests to be acknowledged, include New York City Council President Peter Vallone, Bronx Borough President Frederic Ferrer, U.S. Representative Jose Serrano, Bronx Assemblyman Jeffrey Klein.

**Tentative Agenda**

| | |
|---|---|
| 11:00 | Scheduled start time |
| 11:00 | Irwin Redlener, MD opens the floor, introduces Mrs. Clinton, introduces other speakers, invites Ken Fisher to speak. |
| 11:01 | Kenneth Fisher discusses the genesis of the budget allocation for the New York City Childhood Asthma Initiative. |
| 11:05 | Irwin Redlener speaks of the problems of underserved children, asthma and the need for a children's agenda in New York City. |
| 11:09 | Benjamin Mojica, Acting Commissioner of Health, presents the Department's perspectives on the program. |
| 11:13 | Richard Zahn, president of Schering Laboratories, speaks of the initiative from the perspective of the advances in asthma treatment, and the need to deliver these treatments. |
| 11:16 | Irwin Redlener speaks of bringing the effort to the attention of Hillary Rodham Clinton, and her interest in it. |
| 11:17 | Hillary Rodham Clinton speaks. (CHF to be advised of her point of view.) |
| 11:21 | Conclusion. |
| 11:22 | Questions and answers. |

# # #

New York Childhood Asthma
Inititive Announcement, page 3.

**Other considerations**

1. Will there be limitations to the number of persons allowed within the restricted area? If so, how many people?

2. How far in advance do you need lists of invitees? Do you need both date of birth and social security number? Separate from invitees, presumably employees of the South Bronx Children's Health Center will also need to be cleared, correct? (The Center will be used as an indoor holding station before the event.) What about the days' patients?

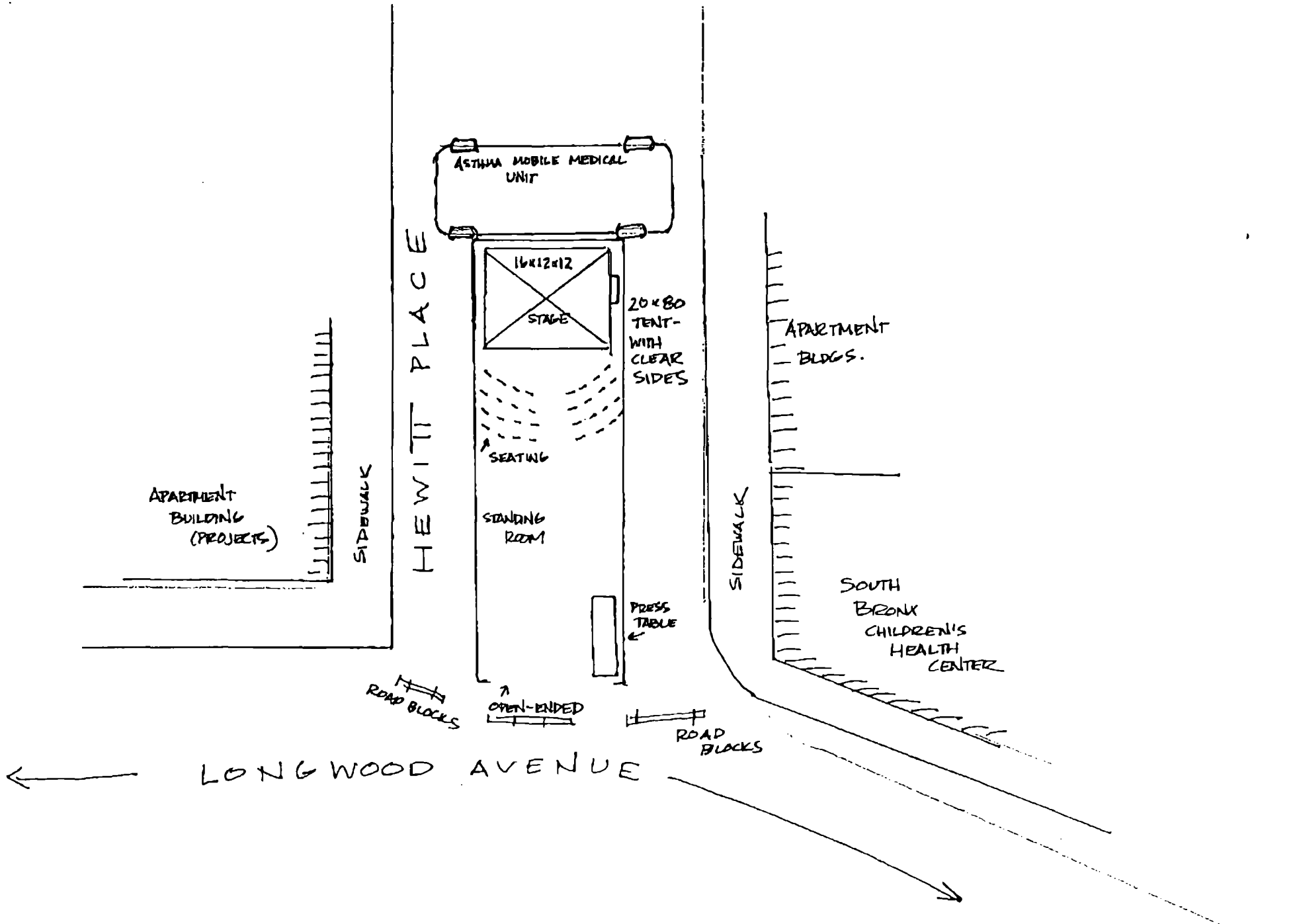
3. Who takes care of street permits (the street will need to be blocked off), we or The White House?

4. What is the general size of a restricted area? (See below)

5. We are intending to set up a large enclosed heated tent for the press conference since it will be outside in the Bronx and it will likely be cold. May we do so re security? The size tent we have in mind is 20 x 60 (to fit approx 100 people and including a stage as shown in att. drawing.)

6. Are credentials issued at the time of the event?

7. What is the protocol for inviting local politicians? Is that done by The White House or by The Children's Health Fund?




LAYOUT (PROPOSED) FOR 12.11.97 (11:00 AM)
PRESS CONFERENCE

MEMORANDUM FOR THE FIRST LADY Nov 25, 1997

FROM: Domestic Policy Staff

SUBJECT: Child Asthma Initiative

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IMPACT

Asthma is a chronic inflammatory disease of the airways. In the United States, asthma affects 14 to 15 million persons. It is the most common chronic disease of childhood, affecting an estimated 4.8 million children with the direct and indirect cost estimated at $6.2 billion dollars in 1993. Over 3800 children and young adults under 25 died from asthma nationwide during the period 1980-1993. 342 children died from asthma in 1993 alone. Asthma is associated with the loss of 28 million activity days annually and 2.2 million pediatrician visits. It is the leading cause of school absenteeism. It has been estimated that among children 5-17 years old, asthma accounted for approximately 10 million missed school days at a cost of $726.1 million in caretakers' time lost from work.

TRENDS

The burden of asthma on the US population is increasing. Through the 1980's, the prevalence of asthma increased 29%, hospitalization rates increased 6% and mortality rates increased as well. The most notable increases were for children and young adults. Hospitalization rates for children less than five years old have increased 57% since 1980. These rates increased at a time when total hospitalization rates for children decreased. Overall, the annual age-specific asthma death rate increased 118% (from 1.7 to 3.7 per million) between 1980 and 1993 for persons aged 0-24. Explanations for rising prevalence, morbidity and mortality are varied. Investigators have attributed increased hospitalization to improved diagnosis, untoward effects of treatment, environmental factors, improvements in vital statistic reporting, and increased tendencies for asthmatic patients to use hospital emergency departments as primary sources of care.

VULNERABLE POPULATIONS

Childhood asthma has become more prevalent and more severe in the last decade, and disproportionately affects minority populations. In 1993, among children aged 5-14 years, blacks were four times more likely than whites to die from asthma.. In the 0-4 age group, blacks were six times more likely to die from asthma than whites. Hospitalization rates are consistently highest among blacks. In 1993, among persons aged 0-24 years, blacks were 3.4 times more likely than whites to be hospitalized for asthma..

Children living in the inner city are particularly vulnerable. New York City has the highest rate of hospitalization and mortality for childhood asthma of any area in the United States. As of 1993, New York City children were hospitalized for asthma at four times the national rate. Within the city, these rates are three to five times higher for African Americans and Latinos than for the rest of the population. Areas in New York City with the highest asthma hospitalization rates include the South Bronx, Upper Manhattan, Central and North Brooklyn. Nationally, asthma rates are highest in New york, Chicago, Fresno, and Maricopa County, Arizona.

The exact relationship between generally known risk factors and the increase in asthma-related morbidity and mortality among minority inner city children has not been determined. Poverty undoubtedly impacts upon the health of inner-city populations. Poverty has been linked to underdiagnosis and subsequent reduced preventive asthma care. Defined risk factors such as passive and active cigarette smoking and air pollution may be greater for minority, inner-city children. Also, infestation with pests such as roaches, mites, rodents and mosquitoes are greater problems among the poor than the more affluent. Finally, socio-economic status has been directly linked to overall compliance and medical follow-up.

PATHOGENESIS AND MANAGEMENT

Asthma results from complex interactions among inflammatory cells, mediators and the cells and tissues resident in the airway. Atopy, the genetic predisposition for the development of a mediated response to common aeroallergens, is the strongest identifiable predisposing factor for developing asthma. In

susceptible individuals, this chronic inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough, particularly at night and in early morning. The episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or with treatment. This inflammation does cause an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.

The effective treatment of asthma is dependent on four components: 1) correct diagnosis of asthma 2) reducing factors contributing to asthma severity 3) pharmacological therapy 4) self-management education.
The goals of asthma therapy are to: 1) prevent chronic and troublesome symptoms 2)maintain normal pulmonary function 3) maintain normal activity levels 4)prevent recurrent exacerbations 5) provide optimal pharmacotherapy with minimal side-effects and 6) meet patients' and families' expectations of satisfaction with asthma care.

NEW YORK CHILDHOOD ASTHMA INITIATIVE

This initiative is organized as a partnership between the office of Councilman Ken Fisher and The Children's Health Fund, with strong collaboration from the New York City Department of Health. The goals of the program are to increase public awareness and knowledge of pediatric asthma and develop programs, models, and policies that will serve to reduce childhood asthma morbidity and eliminate childhood deaths due to asthma. The initiative will give attention to specific communities with high asthma prevalence.

The program components will include a Childhood Asthma Task Force. This task force will be representative of NYC service sector agencies and will be co-chaired by Councilman Fisher and Children's Health Fund President Irwin Redlener MD. Other program components are Childhood Asthma Awareness Campaign and Clinical Programs. These components will include a public information initiative, asthma information hotline and provider education. In addition, the establishment and/or enhancement of primary care programs with special asthma focus will be organized in two communities where asthma is particularly problematic, Hunt's Point and Brooklyn. Existing care centers will provide

needed state-of-the-art asthma care in these two high risk communities and will serve as demonstration sites for a range of clinical and educational programs targeted at childhood asthma.

*TUCSON/ALMATY HEALTHCARE COALITION*

520-324-1784
FAX 520-795-5689

Tucson Medical Center, Arizona Bldg., 2nd floor, 5301 East Grant Road, Tucson, Arizona 85712

# FAX COVER SHEET:

**Date:** 12/4/97

**Number of Pages:**

**To:** Jennifer Klein, Assistant to the First Lady — 202-456-2878

**From:** Emily Jenkins, Project Director — 520-795-5689

**Re:** Asthma Information and Invitation to Speak at Greater Issues Series

Jennifer:

Thank you for your call. Attached is a copy of Dr. Thorpe's invitation to Mrs. Clinton to speak at the Greater Issues Series. We would like to combine this visit with an informational program for Mrs. Clinton on asthma from clinical, research and community perspectives.

I will FedEx a package of information to you next week regarding asthma as a health problem in the U.S., with information on these different areas of the problem.

Emily Jenkins

# TMC HealthCare

December 3, 1997

Mrs. Hillary Rodham Clinton
1600 Pennsylvania Avenue
Washington, DC 20500-0001

Dear Mrs. Clinton:

As an influential advocate for a better world, we ask that you consider sharing your views on social reform – both nationally and globally – in our widely acclaimed speakers program held annually in Tucson, Arizona. Our program, which is sponsored by the TMC Foundation, is 14 years old. Known as the Greater Issues Series (GIS), the program features prominent national and international figures.

Tucson Medical Center (TMC), a community hospital, is the largest medical facility in Southern Arizona. Through relationships with health care providers throughout Southern Arizona and Northern Mexico, we strive to improve the quality of life within our sphere of influence. TMC has a large pediatrics department. More than 4,500 babies are born each year in TMC's Labor & Delivery department. We do extensive work in the area of respiratory ailments, especially pediatric asthma.

We excel in a wide range of health care services, and assure that our services are provided to all, including the uninsured and underinsured. One of TMC's primary missions is to help create a healthier community, and that includes relationships beyond Tucson – and even Mexico.

TMC is the lead hospital in the Almaty, Kazakhstan, health care program, which you visited recently. Almaty Program Director Emily Jenkins is housed in our TMC facilities and is a member of our Communications Team.

We want to thank you for your kind remarks about Tucson during media interviews, and for the interest you expressed to Emily about our asthma projects in Tucson. The University of Arizona has one of the leading programs in respiratory disease. We would arrange a briefing for you regarding the research being done in the respiratory program as part of a GIS visit.

Currently, we are developing an early learning and elder care program for employees and the community, with specific attention being given to welfare-to-work participants. The State of Arizona considers this a model program for other Arizona organizations to emulate. We are hopeful that TMC's work in this area can impact some of the family needs you address in your book *It Takes a Village*.

Communications Team
5301 E. Grant Road ♦ Tucson, AZ 85712
(520) 324-2018 ♦ Fax: (520) 324-2127

The TMC Foundation, which has sponsored GIS since 1983, has attracted distinguished speakers who have had an impact on our community. We would greatly appreciate the opportunity to include your name in that register of eminent speakers: James (Scotty) Reston, Helmut Schmidt, Edward Heath, Henry Kissinger, Jeanne Kirkpatrick, Abba Eban, Peter Ueberroth, Tip O'Neill, Casper Weinberger, Eric Sevareid, Mario Cuomo, George Will, Carl Sagan, Zbigniew Brzezinski, Peter Arnett, William Bennett, Richard Cheney, Elizabeth Dole, Richard Lamm and Shimon Peres.

The GIS format focuses on a single guest speaker, who addresses an audience of approximately 2,000. Before and after the speech, there are receptions/discussions with smaller groups. There also is a brief meeting with the media.

Normally, we set ground rules for the media so that the focus of questions is on the topics addressed during the GIS program. Given your prominence and the news coverage that would be generated by your appearance in Tucson, we would work with your press secretary to manage the media briefing.

GIS speakers who were in office -- or a spouse of someone in office -- when they spoke in our program include: Mario Cuomo, governor of New York at the time; Zbigniew Brzezinski, who was a member of the President's Foreign Intelligence Advisory Board; and Elizabeth Dole, whose husband, Bob, was in Senate leadership.

Enclosed is our recent report to the community, which provides a brief overview of the work we do at TMC.

If you need more information, please have someone on your staff contact us. If you decide to participate in our GIS program, we would hope that it could be during the first quarter of 1998. We are more than willing to work around your schedule and help with any special arrangements that you need.

We look forward to hearing from you.

Sincerely,

Darrell P Thorpe

Darrell P. Thorpe, M.D.
President and Chief Executive Officer
TMC HealthCare

CC: Patti Solis-Doyle, Director of Scheduling
Mona Pasqael, Western Political Director
Emily Jenkins, Almaty Program Director

Enclosures

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