AMERICAN HEALTH CONSULTANTS®

TB MONITOR™

The Monthly Report on TB Prevention, Control, and Treatment

INSIDE

JULY 1999

VOL. 6, NO. 7 (pages 65-76)

American Health Consultants® is A Medical Economics Company

Twice-weekly RIF/PZA may get nod as six months of INH gets more respect

Writing group labors over final details of CDC/ATS preventive therapy

As TB experts continued sorting out the details of what will become the new guidelines for preventive therapy, two new additions to the still-evolving document had emerged. First, twice-weekly rifampin / pyrazinamide (RIF / PZA), not listed as an option in earlier drafts, got to come in from the cold; second, six months of isoniazid (INH), formerly relegated to a footnote, made it back on the table of numbered options.

If those changes stick, it would mean the list of choices for treatment of latent TB would include all of the following: nine months of INH, either daily or twice-weekly; six months of INH, either daily or twice-weekly; two months of daily RIF / PZA; two months of twice-weekly RIF / PZA; and, in certain situations, four months of rifampin (RIF).

The "writing group" charged with working out the details is composed of TB experts from the Atlanta-based Centers for Disease Control and Prevention (CDC) and from the American Thoracic Society. The document is due out in about six months.

> **"I assumed they'd endorse this regimen to begin with, and I was shocked when they didn't."**
> **Richard Chaisson, MD**

Many TB controllers said they were pleased with the changes. "Wow! That really makes my day," says **David Ashkin**, MD, medical adviser to Florida's TB control program. Ashkin will use the twice-weekly short-course regimen in controlled clinical trials in the state. "It makes total sense, but it needs more study, which is exactly what we're doing. I'm glad they approved it."

Probably no one has lobbied harder for twice-weekly RIF / PZA than **Richard Chaisson**, MD, assistant professor of medicine at Johns Hopkins University in Baltimore. "I assumed they'd endorse this regimen to begin with, and I was shocked when they didn't," he says.

There are two reasons Chaisson says he'd like to get his hands on the regimen. First, it's by far the most feasible way to get preventive therapy into a population of injecting drug users (IDUs) in Baltimore; in the community setting, direct observation of IDUs would be hard to pull off more than twice a week, he says.

And among the prison population — the second group targeted as a top priority for preventive therapy — more than twice-weekly would be virtually impossible, he adds. "Prisoners are an important population," he says. "But at the detention center here in Baltimore and in the state prison system as well, providing *anything* on a daily basis is very, very difficult, which is why I've lobbied so hard for this."

In Massachusetts, where TB controllers have targeted the foreign-born (not IDUs or prisoners) for preventive therapy, it's a different story. Given PZA's reputation for unpleasant side effects and the longstanding reluctance of most foreign-born communities to buy into the notion of any kind of preventive therapy, Nardell thinks four months of RIF is the logical first choice.

"From the standpoint of compliance, we haven't had any more success with RIF/PZA than with six months of INH," says Nardell. "People here simply don't seem to be tolerating it very well. Four months of rifampin, on the other hand, seems acceptable on every count, so why make us go through the back door to get to it? Why save it for special occasions?"

Complexity issues still troubling to some

Foreign-trained physicians and their foreign-born patients have a tough time accepting American beliefs about skin testing, the BCG vaccine, and regular isoniazid prophylaxis. Does throwing in a long list of new options, some complicated by potential side effects, sound like a good idea? Nardell thinks not.

As long as he has access to twice-weekly RIF/PZA, Chaisson says he has no reservations at all about four months of RIF. "Of course, there's only that one study of the Chinese silicotics," he says. "But to me, four months of rifampin is a perfectly fine regimen." For that matter, he adds, why not just three, which was the duration of the Hong Kong trial?

The decision to put the four months of RIF into a special-occasions straitjacket because it lacks sufficient data credentials is especially needling to Nardell. "When you confine your choices exclusively to this 'evidence-based' medicine, you can tie yourself in knots," he says. Better to let a little common sense prevail, he adds.

Chaisson says he's sympathetic, seeing as how twice-weekly RIF/PZA was probably snubbed the first time out because it had never gone head-to-head in a clinical trial against the daily form of the regimen.

Insiders at the CDC allow that if Chaisson had made it to the first working group, twice-weekly RIF/PZA probably would have been on the list from the start. As fate would have it, Chaisson was stuck in Baltimore, laboring over a grant application involving a trial of — you guessed it — twice-weekly RIF/PZA. He got the grant.

As for six months of INH (both twice-weekly and daily variations look set to get the nod), that shift is one most clinicians seem to endorse without reservations.

"There's been a lot of debate over this," says Chaisson. "Health departments say, 'Gee, six months is already too much work; no way we can do nine.'" Others argue that from the standpoint of an individual patient, it's clear nine months is better.

Both sides are correct, Chaisson points out; but what the data show, he adds, is that what's best for one patient doesn't work as well in an entire program. It follows that the best choice is to provide lots of choices, so programs and individual physicians can make their own decisions, he adds.

The thought of so many choices still gives Nardell the fidgets. "First they tell us treatment of latent TB should go out of the public health clinic and into the community," he grumbles. "Then they give us not one option, but three or four. In the community setting, that's too complicated — more complicated drugs to learn about and more drugs, period."

Chaisson disagrees. "I worry when I hear people say 'make it real simple,'" he says. "You do that, and you lose options." ■

COMING IN FUTURE MONTHS

- Is DOTS enough in Africa?
- Kosovo refugees in the United States
- Pockets of TB increase in Japan
- Highlights from the ACET meeting
- Infection control at outpatient clinics

Big funding package promised for border

TB control is just the start, officials say

Late last month, when American and Mexican top-level officials signed their names to a document that will commit USAID to providing a $10 million funding package earmarked for cross-border TB control, **Bill Archer**, MD, the Texas Commissioner of Health, wasn't there.

That's surprising, considering it was Archer's arm-twisting that convinced USAID to cough up 10 times the amount the agency originally had budgeted for TB control on the border. Instead, Archer, son of the powerful chairman of the House Appropriations Committee who shares his name, was doing what his staff say he likes doing best: hanging out at a three-day state health department conference in San Antonio, talking to people.

"Oh, man, does he love talking to people. In fact, he talks too much," says **R.J. Dutton,** PhD, director of the Texas Health Department's Office of Border Health and one of Archer's most fiercely loyal employees. "What he likes is to get out there and engage people one-on-one," Dutton adds. "It's one of his biggest strengths."

It's an issue of trust

Archer, who is fluent in Spanish and served as a medical missionary in South America before he was appointed to his current post, has been talking to Mexican health officials for the last three years, trying to win the trust he says had to be there before anything else could happen.

"It's easy to think you can build a bridge across a cultural divide, but it's not a simple thing," Archer says. "Because of that kind of trust and commitment, Congress finally was willing to justify the kind of investment USAID is about to make in Mexico to improve TB control there."

In true Texas spirit, Archer sees no reason to stop with just a big package for cross-border TB control. Across the same cultural bridge, he envisions a whole gang of fellow travelers, including cross-border programs for rabies, neural-tube defects, diabetes, dengue fever, and environmental issues, along with beefed-up programs for surveillance and epidemiology and more binational sharing of data.

In this, Archer has the support of another son of a well-connected guy, Texas Gov. George W. Bush, says Archer's chief of staff, **Jacquie Shillis**. "Gov. Bush very much wants projects for TB and diabetes on the border," she says. "As he sees it, we're connected to Mexico historically and economically; the part of our population that's Mexican-American is large and growing. So it's imperative that the two countries have a good relationship."

Only one hitch still to resolve

The only hitch is how to make sure the money stays where Archer is determined it will: on the border, and not go into TB control in other parts of Mexico such as the Baja peninsula, for example, or along Mexico's southern border with Guatemala.

Strictly from a programmatic point of view, confining the money to the U.S./Mexican border makes the most sense, Archer contends. "For one thing, $10 million isn't enough to make a difference in an entire country," he says. Plus, he adds, the border is unique — a Tex-Mex hybrid that's neither one nor the other and has special problems that deserve customized solutions.

From a political perspective, things aren't that simple. "If Congress perceives that [US]AID is unable to accomplish this significant investment on the border, they'll be frustrated," Archer says. "If Mexico perceives that all the money is going to the border, which is their richest region, well, then they'll have political problems."

It's a difference that still has to be worked out, but Archer thinks it can be. "Both sides are committed to working out the differences," he says. "I've got some ideas."

Archer's ideas about TB control have their origin in what he experienced as a volunteer for Project Hope, a nongovernmental organization that recruits physicians willing to volunteer their time helping train health providers and build sound health policies in developing countries.

During a stint in Kazakstan, where he was working as an obstetrician/gynecologist, Archer says he was struck by the enormity of the country's TB burden and the scarcity of resources available for fighting the disease. At one point, moved by TB patients' plights, Archer took over the care of 50 or so of the nation's most intransigent cases. For some patients, four drugs and direct observation did the trick; but for about a dozen patients, it would take expensive

***TB Monitor* profile**

A favorite son in Texas on power and its uses

Not surprisingly, **William Archer III**, MD, the Texas Commissioner of Health and son of the chairman of the powerful House Appropriations Committee, Rep. Bill Archer (R-Texas), says there are both pluses and minuses that go with having a well-connected father.

"There are folks who say you're here because of your dad, that you don't know anything about public health. You have to overcome those perceptions," he says. There are privileges, too, but they come with a price, he adds. "I want to be known for my own skills, not because I'm the son of somebody."

Growing up, Archer says he developed what he now sees was a typically American outlook on life. "We Americans base things on knowledge. It's not that we don't value relationships," he says. "It's just that we tend to value knowledge more. It's what we lead with."

A few years spent volunteering his services as a physician in developing countries was a powerful object lesson in humility, he says. "Here I was, trying to have an impact on communities; but I was finding that knowledge alone didn't make an impact," he says. "It was relationships that made an impact. Then, the knowledge could begin to flow."

Eventually, Archer came to understand other facets of the Latin culture as well. "In South America, I didn't have any of the labor-saving machines all of us here take for granted," he says. "Instead, I walked to the market, bought food, cooked, washed the dishes in a little sink that stood in one corner of my room. But it was the weirdest thing: I felt like I had all the time in the world."

Archer has been strongly influenced by the philosophy of financier / philanthropist George Soros, who has written that as a young man he was struck by how some kinds of "knowledge" — people's best-considered decisions about what stock to buy, for example — not only reflected their version of objective reality, but shaped and altered reality as well.

The same rule applies in social and political settings, the Soros philosophy goes. Too often, Archer says, Americans ignore that verity.

When it comes to the border, Archer evinces a special affection for it, where the two cultures and peoples — the north, with its respect for knowledge, and the south, which cherishes relationships —meet and meld. "The border is really its own place," he says. In south Texas, settlers of European origin have rubbed shoulders with Mexicans as far back as the 1500s, he points out.

"Families have always lived, worked, shopped, and obtained their health services on both sides of the border," he adds. "It's really only national laws that prevent it from being a lot more unified than it already is."

Sometimes, Archer says people ask him whether the border is more Mexican or more American in character. "I don't know," he tells them. "It's neither — a hybrid," a word some people might use to describe Archer himself. ■

second- and third-line drugs, which Archer purchased with money he wrangled from USAID. Altogether, he achieved a 90% cure rate, "battling physicians there all the way," he says. The headiness of his accomplishment is still audible in his voice when he talks about the experience.

Next came a stint for Project Hope in South America. At about the same time, Archer also began serving as a representative for Project Hope at Ten Against TB (TATB), a binational coalition founded three years ago to address cross-border issues in 10 counties and Mexican departments that line the southern U.S. border.

Though chronically underfunded and top-heavy with officialdom and bureaucrats from both countries, TATB nevertheless created a place where Archer and others could begin to reach across the cultural divide. "TATB absolutely laid the foundation for everything that's happened since," says Shillis.

The upshot of all this was a man with a self-confessed "passion for TB." As soon as he was appointed health commissioner in 1996, Archer formed an internal working group at the health department and told the group to get to work on Washington policy-makers. At the same time they were convincing Congress that the border deserved more attention, they were

charged with finding some governmental or nongovernmental agency that would provide the necessary funding, Shillis says.

Hearkening back to Kazakstan, Archer's inner radar steered him toward USAID. But there, a former head of the development agency strongly disliked the notion of spending taxpayer dollars on TB projects on the border. By the time the House Appropriations Committee was finished, the situation looked bleak. Language approved for appropriations allotted a measly $1 million for a TB project, plus a report on the work.

"When I read that, I figured we'd lost," says Dutton. Undeterred, Archer went to work. The state's newspapers continued to trumpet news of a $10 million aid package whose arrival suddenly looked unlikely. Archer caught a plane to Washington; once on the ground in the nation's capitol, he started talking.

"My dad has never talked to [US]AID — he's not that heavy-handed," Archer says. "But there's no question he's helped open doors for me. He'd say, 'Sure, you can go talk to Sonny Callahan, the Alabama Republican who chairs the Appropriation Committee's Foreign Operations Subcommittee. But he'd never go to Callahan himself and tell him what to do."

A $10 million delivery

Then, one day, as R.J. Dutton recalls, a staffer in the health commissioner's office picked up a phone and found himself talking to Paul White, head of USAID in Mexico. The tide had turned.

By the time Archer was schmoozing the audience at the three-day health conference, White had come up to south Texas, talked to docs and administrators there who knew the border and its issues, formed a binational task force with the Mexican government, toured Mexico, and cobbled together a memorandum of understanding between high-level officials in both countries. Dutton says he remembers with crystal clarity the day he was sitting in a meeting with White and others, listening to speakers drone on, when, almost as an afterthought, White asked Archer how he would like the $10 million delivered.

My God, R.J. Dutton remembers thinking, *they're cutting the deal right here in front of me.*

To Archer, though, the defining moment arrived on another day. Archer, White, and Annette Riggio, a former head of TATB, were in Mexico City with a copy of the language that was to go into the appropriations bill. They needed to know for certain whether Mexico could pledge its willingness to accept the aid package and work with the United States to fight TB but on what had to be, at bottom, essentially American terms?

The answer was yes. So far, says Archer, the bridge of trust between the countries is still holding. ■

The new skin-test diet: An ounce of prevention

Otherwise, skin testing is just a waste of time

Sometimes, less is better. Take Miami for example, where **David Ashkin**, MD, medical adviser to the state's TB control program, thinks it might be best to resist the urge to pile on more infrastructure and more mandates for screening. In fact, Ashkin says he may try to persuade county TB controllers to put existing screening programs on a diet, at least until their usefulness has been determined.

That means resisting the city's current appetite for more — more TB skin testing in the schools, more on the job site, and more among patients of clinicians who serve the private sector where, for example, one concerned pediatrician recently called for city kids to be skin-tested at least every three years.

The call for action comes in the wake of two widely publicized cases of TB: one at a city-run youth center, the other at a Miami Beach elementary school. Contact investigations, though they turned up no evidence that anyone had been infected recently, revealed that roughly one in seven children and teachers at the elementary school were tuberculin reactors, a proportion county health authorities pronounced to be perfectly normal for that population.

"What we really need to be talking about right now is not screening more people," says Ashkin. "The issue is how to get more people who've been screened to start preventive therapy and then finish it. Otherwise, it's all just a waste of money."

A high incidence of HIV infection, a big foreign-born population, and crowded living conditions have helped push the city's morbidity rates to about twice the national average (15.5 cases

per 100,000 in 1997). Between high incidence and an overflowing pool of latently infected people, the city poses "a dilemma that's almost unique in this country," says Ashkin.

A look at Dade County school system demographics is illuminating. Students hail from more than 100 countries, often places where TB is endemic; about half are Hispanic, with African-Americans kids making up the second-highest representation. Although no one keeps tabs on how often, school officials say children and their families frequently travel back home to see friends or family.

Despite, or maybe because of, the exceptionally high background rate of tuberculin reactivity among students, resource limits make a notion like school-based prophylaxis almost laughable. No regularly scheduled health care service is provided in 174 of Dade County's 292 schools; in the remainder, a nurse is available one day a week, says **Nancy Humbert**, director of the county's school health program.

There's a possibility, though apparently not a strong one, that the state's new secretary of health might provide schools with a few more pairs of hands, health department officials say. "That is our dream — to have a nurse in every school," sighs **Eleni Sfakianaki**, MD, medical executive director of the county health department.

Schools should pick up the tab

Other TB control measures now on the table at the health department include mandating more TB skin testing for school children; now, kids must be tested once only, upon entry to the school system. Plus, since the case at the elementary school involved a staff member, not a student, others have mulled over the proposition that the county school should act like any other employer and foot the bill for testing its own employees on a regular basis.

Ashkin, if he gets his way, says he plans an all-out educational assault aimed at convincing physicians and communities of the merit of preventive therapy. For physicians, in particular, that will mean explaining the American take on the efficacy of the BCG vaccine and the vaccine's effect on tuberculin skin testing.

Meanwhile, the Dr. Ashkin skin-test diet works like this: "If you can't [provide and] finish preventive therapy, we're almost to the point of saying don't screen at all." ■

Where a select few know your name — and history

Controllers could find AWOL patients in registry

A nationwide listing of the names of TB patients who've skipped town could save TB controllers a lot of trouble down the road. That conviction has some TB experts in the country calling for the creation of an "AWOL TB patient registry," as the concept has been dubbed.

"If you get a patient and he's new in town, the logical question is whether someone else is already treating him," says **Jon Tillingham**, MD, Oklahoma's TB controller. "If you can't get anything out of him, but you had a database where you found him listed, all you'd have to do is make a phone call."

"We all have a sense that certain patients are more likely to disappear than others."

As many as a fourth of all patients who default from treatment might qualify for membership in such a registry, he says. "Probably 75% to 80% of noncompliant patients will tell you, later if not sooner, if they've been on therapy somewhere else," he says. The rest won't, either because they don't want to or because mental illness in one form or another prevents them from doing so."

In Oklahoma, TB controllers recently spent four months hunting for a patient who'd taken off, it turned out, for San Antonio. "We don't know if he was seen by anyone there or not," says Tillingham, "but if he was, having this registry might have simplified things."

Randall Reves, MD, the medical director of Denver's TB control program, also likes the idea of the AWOL TB patient registry. "We all have a sense that certain patients are more likely to disappear than others," he says. "Especially with the chronically mentally ill, there's good reason to be concerned about how good your health history is."

How soon someone missing from treatment would be eligible depends on the case, adds Reves. "If they've only completed a week of therapy, and they're still infectious, and your sense is that they've left town, I think I'd probably put them in."

Neither TB controller thinks the registry would pose a threat to patients' privacy because

safeguards presumably would be installed to bar anyone except legitimate users. Still, a few other considerations would need careful attention, they say. For one thing, TB controllers who used the registry would need to make sure they were justified in posting someone's name. "You wouldn't want somebody to get snagged by mistake — jerked off a plane or something," says Reves. By the same token, even those who deserved their spot on the registry would need to be taken off once they'd completed treatment.

How long could someone's name reasonably remain on the list? "Maybe after two years you'd take them off and put them into a sort of archive," Reves suggests.

The only detail yet to be worked out (in the minds of registry proponents, at least) is the question of who actually would maintain such a registry. It can't be the Atlanta-based Centers for Disease Control and Prevention because that entity is empowered only to tally numbers of TB patients, not collect their names. Maybe, says Tillingham, the most logical place to house the registry might be with the National TB Controllers Association (NTCA), also in Atlanta.

Though support for the idea of creating the registry seemed strong enough when it was first broached in a committee meeting, NTCA members gave it only a "lukewarm" reception later, says Tillingham.

"I think that may have been the lateness of the day," he adds, more than the merit of the idea. ■

NCET, restored to life, gets busy in new places

May be the right entity to give states a kick

With a new office, a fresh injection of funding, and a restored sense of mission, the National Coalition to Eliminate Tuberculosis (NCET) has given itself some homework: Put a face on TB. **(See related story, p. 72.)**

"We need to figure out what it is people see when they hear the word 'TB' and then develop a consistent image, "says **Fran DuMelle,** national executive director of the American Lung Association (ALA) and longtime adviser to the newly revived coalition.

What that face will look like isn't clear. Still, when it comes to the media or a visiting member of Congress, there are certain things best left unspoken, DuMelle said earlier this year in an address to the Advisory Council to Eliminate Tuberculosis: Please, no lab animals, and no need to mention outbreaks. On the other hand, she added, do try layering TB on top of more consumer-friendly issues, such as clean air.

The target of such messages has shifted, too, from federal to state and local levels, DuMelle says. That shift reflects not so much despair at yet another year of level funding from Congress as it does a growing sense that it's high time states and locals took up some of the slack.

States can't assume Uncle Sam will do it all

"People need to know there's more to TB control than just grants from the federal government," says **Lee B. Reichman**, MD, MPH, executive director of the National TB Center at the New Jersey School of Medicine. "We can't have states think that they can just stop funding TB control programs, and the national government will take care of it. What we need is more political will at the state level."

That said, a logical question might be to ask why NCET just packed up its New York office and moved to Washington, DC? Well, explains Reichman, it's because that's where you find the people who know how to do the lobbying; in particular, DuMelle. "From a staff point of view, Fran knows more about TB than anyone in the country," he says. "No. Make that anywhere on earth."

The move to Washington can only be regarded as a step up. NCET's life in New York was, for a time, the bleak existence of an orphan child. Looking after its needs was a single harried ALA staffer preoccupied with five or six other full-time jobs. There was no money once a grant from the Robert Wood Johnson Foundation expired. Nor was there much action, given that last year's only scheduled meeting was called off and NCET's four task forces had ceased operation.

At one especially low point, NCET found its head on the chopping block, awaiting the results of a survey DuMelle mailed out: Should the ALA pull the plug or try to resuscitate the ailing coalition? Luckily, 90% of poll respondents gave it a thumbs-up, DuMelle says. "After some arm-twisting from Reichman and others, ATS agreed to provide financial support plus the full-time services of a staffer who could fire off action alerts and keep track of pending legislation. ■

'Face of TB,' as seen in Sunday *NY Times*

One person more memorable than 'a million'?

When readers opened their *New York Times* Sunday magazine on May 30, they found a big, heart-tugging article about a young Thai refugee undergoing treatment for multidrug-resistant TB at National Jewish Hospital in Denver.

The patient whose ordeal was recounted, a 19-year-old who'd probably contracted a highly resistant form of TB from his father (who, in turn, likely had experienced erratic treatment in his homeland), endured a lobectomy, a pneumectomy, and finally a thoracoplasty, all the while enduring the harsh side effects of second- and third-line drugs.

Lisa Belkin, the *New York Times Magazine* contributing editor who frequently writes about health care issues, says she found researching the piece distressing and alarming. "I'd written a lot about the 1991 TB outbreak in New York City, so some of what I learned didn't take me by surprise," says Belkin. "But to find that we're actually moving backwards in time and that doctors are having to resort to surgery again to try to cure their patients — that just blew me away."

One patient's story

The inspiration for the piece was a phone call; in this case, from a friend who'd heard about an engaging young patient at National Jewish. "[The patient] said he wanted to tell his story," says Belkin. "Sometimes all you have to do is ask."

What she liked best about doing the story was the chance it gave her to make TB real for her readers, she says. "I liked the opportunity this gave to put a face on TB."

"I don't know if it's American society in particular or human nature in general, but we only tend to absorb information we can put a face on. If you say 'millions,' those millions aren't me. But you meet one person, and that person could be you."

Some of the TB experts Belkin spoke with worried that her blunt descriptions of the side effects of second- and third-line drugs might frighten patients out of compliance. Others worried that her writing about TB among the foreign-born might provoke anti-immigrant sentiments.

"But these drugs really can be brutal," she says, referring to the first objection. "And it's like one physician I talked to put it: 'We can't close down our borders even if we wanted to, so we'd better get on with it and do something about global TB.'" ■

Basic training starts for Russian project

Russian physicians see DOTS-Plus in action

Last month, a group of physicians from prisons in the Russian province of Tomsk arrived in the United States prepared to become the first people on earth — outside the small corps of Harvard TB experts who pioneered the concept — to learn the nuts and bolts of DOTS-Plus, the controversial variation of Directly Observed Therapy, Short-Course.

The notion that patients can be treated successfully with expensive, brutally toxic medications under Spartan field conditions is one that still provokes skeptical opposition among many respected TB experts.

"I'm not saying I'm against DOTS-Plus, just that it's fraught with some terrible problems," says **Gwen Huitt**, MD, co-director of the adult day unit at the mycobacterial division in the department of medicine at National Jewish Hospital in Denver. "Part of me thinks if you're working in a developing country, and you've got drug-resistant cases, the best thing is to put these people in a sanitarium. Treat them as best you can, isolate them, but don't start these second- and third-line drugs."

MDR patients can't be left to die

DOTS-Plus proponents passionately disagree. Allowing MDR-TB patients to die for lack of treatment — the kernel of realpolitik believed to make DOTS sustainable in even the most impoverished countries — is not only unethical, they contend, but eventually will lead to the takeover of resistant strains. "The point is that DOTS is fine as far as it goes, but if you give it to someone with resistance, you'll just get more resistance," says **Lee B. Reichman**, MD, MPH, director of the

National TB Center of the New Jersey Medical School in Newark.

Newark was the first stop on the Russians' itinerary. Under the tutelage of experts at the center and speaking through an English translator, the group spent last month learning the nuts and bolts of how to treat MDR-TB. "They're all extremely bright and capable, and they're asking very good questions," Reichman reports. Among those questions was what to do with a patient on six liver-toxic products.

After Newark, the Russians were scheduled to leave for Lima, Peru, site of the model DOTS-Plus project, for a close-up look at the program.

"The meds we use get a lot of really bad press. They're not easy to take, not by any stretch," admits **Jennifer Furin**, MD, PhD, a veteran of the Lima project and the director of clinical services in the program of infectious disease and social change at Harvard University in Boston. "But what we're finding is a relatively new concept in TB treatment — that it's possible to treat through a lot of the side effects."

Treating around side effects

"Side effects" is putting it mildly. To begin with, there's cycloserine. "You mention cycloserine and people say, 'Oh, you can't possibly use that medication; it makes everyone crazy and they have seizures,'" says Furin.

According to Huitt, in fact, 80% to 90% of patients on cycloserine suffer side effects. "For some, it's just mild depression and trouble with tasks like balancing a checkbook," she says. In other cases, the drug has provoked suicide.

Then there's ethionamide, which causes severe gastrointestinal distress, including nausea, vomiting, and diarrhea. In addition, ethionamide often leads to endocrine dysfunction, which can manifest itself as drug-induced diabetes, impotence in men, or menstrual irregularities in women.

Para-Amino Salicylic Acid, or PAS, is infamous for the bloating and diarrhea it causes; taken in combination with ethionamide, it's a sure-fire guarantee a patient will experience hypothyroidism, Huitt says.

The drugs are as tricky to administer as they are hard to tolerate, Huitt adds. PAS must be taken with an acidic beverage, never with anything alkaline, not even water. Quinolones demand an empty stomach; plus, patients must avoid taking antacids, multivitamins, or anything else that might contain a metal, which would inactivate the drug. "The whole thing is just a can of worms," says Huitt. "To be honest, there aren't even that many people in the U.S. who can work with these drugs."

Furin and her colleagues say they've learned to manage. "The way we look at it is that treatment for MDR is a lot like cancer chemotherapy," she says. "We train our health care workers to think about the drugs that way, so that they learn how to manage both the psychological and physical impact."

Along with providing support and monitoring carefully for compliance, community health workers in Peru look carefully for early signs of trouble, says Furin. The trick is to figure out which symptoms are unpleasant but manageable, and which ones signal life-threatening conditions, such as hepatotoxicity or renal failure.

Serious side effects are rare, she adds. "I can count on my fingers the number of times I've had to stop a drug." Other reactions haven't been as bad as experts had warned. "We found when we started doing this work that most of the literature on these drugs' side effects comes from the 1960s," she says. "There was a lot more fear about the subject than there was real data."

Though experts predicted practically all patients on cycloserine would suffer seizures and psychosis, Furin says she's found the incidence of those symptoms is closer to 6% for seizures and 8% for psychotic symptoms. Renal failure occurs only about 2% of the time. Instead of 100% of patients on PAS and ethionamide suffering from hypothyroidism, Furin says the true proportion, in her experience, is closer to 30%.

Counter side effects early

Even when serious side effects do occur, DOTS-Plus practitioners argue against lowering dosages or dropping a medication. "Instead, we try to recognize side effects early on and treat them as aggressively as possible," Furin says. "That's the kind of thing the Russian doctors need to see."

After Peru, the Tomsk physicians will spend the last leg of their journey in Birmingham, AL. There they'll get further instruction from Michael Kimerling, MD, MPH, the medical director for the Russian program of the Public Health Research Institute and consultant for the medical arm of Doctors Without Borders. ■

BCG's lost 'luggage' may hold a big key

Research holds up genomes and finds lots of holes

A new series of genetic analyses of BCG holds out hope that scientists will someday understand what's so baffling about the bacille of Calmette and Guerin: That is, why did it perform well in one trial, so badly in another, and at middling points in the rest?

Researchers recently announced they had found that in its journey through time, the BCG vaccine or, more precisely, the vaccine's 13 "daughter" strains lost lots of genetic baggage.

Whether something important and protective was tucked into the missing bags isn't certain, says **Marcel Behr**, MD, assistant professor of medicine at McGill University in Montreal. But clearly, some baggage has been lost.

Freeze-drying keeps genetic material intact

For example, Behr found that BCG-Pasteur — the strain maintained at the Pasteur Institute in France — has undergone four genetic deletions, on four occasions, between 1908 and 1961. Shortly thereafter, a way to freeze-dry the strain was perfected, a development which presumably put an end to subsequent large-scale losses of genetic material.

Extrapolating from that kind of evidence, Behr says most "younger" daughter strains that existed earlier in time would have lost less genetic material than their "older" sibling strains used in later trials.

For example, it's known that one of the daughter strains used in the American Indian trial, where the vaccine performed excellently, also was used in Chingleput, where the vaccine disgraced itself. "We know the BCG-Pasteur strain of the 1930s had changed by the time the Chingleput trials took place," Behr says.

As for the "mother" strain, it has vanished in a fire. Little can be said for certain about this departed family matriarch, Behr adds. "You can read the studies, but the way studies were carried out in the '20s, '30s, and '40s is not the way they are done today. And in some ways, even the people who got the vaccines in the '30s and '40s are different from people today."

Working with colleagues, among them Peter Small, MD, assistant professor of medicine in the division of infectious diseases at Stanford University Medical Center, Behr accomplished two notable feats in his latest round of work on BCG. First, he compared the genome of BCG to that of M. tuberculosis; second, he compared the 13 daughter strains available today with M. bovis, the member of the complex that was attenuated to form the original culture.

In their comparisons, the researchers turned up many differences: genes present here but missing there, genes absent here but present there. "We've only shown changes in *some* of the 13 BCG strains," Behr adds. "But one can only suspect that each strain has undergone its own evolution."

If true, that wouldn't necessarily cancel the long-cherished supposition that cross-reactions from ambient tropical mycobacteria make BCG lazier, if you like, as it draws closer to the equator, the so-called "southern hemisphere/northern hemisphere disconnect." It only sets forth a second hypothesis, this one backed by a new study's evidence.

To bring about BCG's genetic evolution, two kinds of forces were probably at work, Behr says. On one hand, the bug may have adapted passively to laboratory conditions; on the other, active pressures from manufacturers and consumers of the vaccine may have forced certain genetic changes.

One variety of active forces known to have been at work was the demand for a vaccine that reliably converts the tuberculin skin test. Why hope for an outcome that renders the skin test incapable of saying clearly whether or not recent infection has occurred? Well, says Behr, because tuberculin reactivity, along with relative lack of virulence, are the two traits prospective buyers got in the habit of wanting in their BCG vaccines.

BCG batches that failed the tuberculin reactivity test could be counted on to be returned to their manufacturer, perhaps with a nasty note enclosed; that meant the pressure was on to make sure that whatever else it might do, a BCG vaccination would cause a skin test to react positively.

The same goes for a tolerable level of virulence: Countries that found their BCG shipments provoked big suppurations on the arms of recipients typically sent back their products and asked for a refund. The end result, Behr adds, is a bad joke of a vaccine — one that usually messes up the tuberculin skin test and is mild-acting enough to offer what appears to be little protection.

On what he calls a "micro" level, individual labs probably also tweaked their seed lots in various ways. For sure, scientists are known to have fiddled with one strain to make it less apt to die in the process of being freeze-dried. Did that alter the protective ability of the lots? "There's no way to know," he says. "All we can say is they were selecting for mutants that were more tolerant of being frozen and dried."

The genetic variations Behr and Small turned up suggest a number of starting points for how BCG might be restored to its best-ever levels of usefulness, which, after all, have never been measured at more than somewhere between 70% and 80%, Behr adds. The work also suggests places in the genome to go looking for genes for virulence and attenuation. "By learning about the differences, we also might find out whether one of the currently available BCG strains is better than the others," he says. "So we could at least recommend using the best BCG."

Behr acknowledges his indebtedness to the scientists at the Pasteur Institute, who carried out the mammoth genome-sequencing project and then shared it with the world. He also pays homage to Stanford researchers who devised the technology for the DNA micro-array.

"When you do a Southern blot," he explains, "you take a couple of micrograms of DNA and you ask, 'Is this gene present or not?' But when you make a micro-array, you make 5,000 small [representations], one for each gene of the genome, and ask: 'Which of these 3,924 genes is absent? Which is present?'" ■

Final OSHA TB reg may be issued by year's end

Annual TB mask fit-tests may be required

The Occupational Safety and Health Administration (OSHA) may issue the final version of its much-debated tuberculosis standard by year's end, an OSHA official has reported.

"We haven't set a hard-and-fast date, [but] we are shooting for the end of the year," says **Amanda Edens**, MPH, industrial hygienist in the OSHA health standards program in Washington, DC. The Office of Management and Budget will review the final version of the proposed rules, which drew

CE objectives

After reading each issue of *TB Monitor,* health care professionals will be able to do the following:

- Identify clinical, ethical, legal, and social issues related to the care of TB patients.
- Summarize new information about TB prevention, control, and treatment.
- Explain developments in the regulatory arena and how they apply to TB control measures.
- Share acquired knowledge of new clinical and technological developments and advances with staff. ■

TB Monitor™ (ISSN# 1082-8664), including **Common Sense about TB™** and **TB Guide for Health Care Workers™**, is published monthly by American Health Consultants®, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodical postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **TB Monitor™**, P.O. Box 740059, Atlanta, GA 30374.

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hundreds of comments and testimony in a series of national hearings.[1]

Among the issues will be whether the final OSHA regulations diverge too greatly from TB guidelines by the Centers for Disease Control and Prevention, she says.[2]

"I don't think that is going to be the case," Edens adds.

While emphasizing that no final decisions have been made about the content of the final standard, Edens shed a little light on recent discussions about fit-testing of TB N95 respirators.

Jury still out on respirator fit-testing

A recently published government study underscored the efficacy of TB respirator fit-testing programs, but there was some question whether annual fit-testing would be required in the final standard.[3]

However, because annual fit-testing is required in OSHA's respiratory protection standard, the agency would have to determine that there is something "compelling" about TB or health care workers to leave that requirement out of the TB standard, she explained.

"I think what is before the agency now is that since we have already made the decision that annual fit-testing is an important element to have, is there some reason why TB is different from other agents or chemicals that [annual] fit-testing isn't necessary?" Edens says.

In addition, Edens clarified that annual TB respirator fit-testing is currently not required.

"We are using the old respiratory protection standard to handle TB now while we are in the process of doing the final TB standard," she says. "The old respiratory protection standard, which has been recodified [as OSHA standard # 1910139], does not have an annual fit-testing element in it."

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