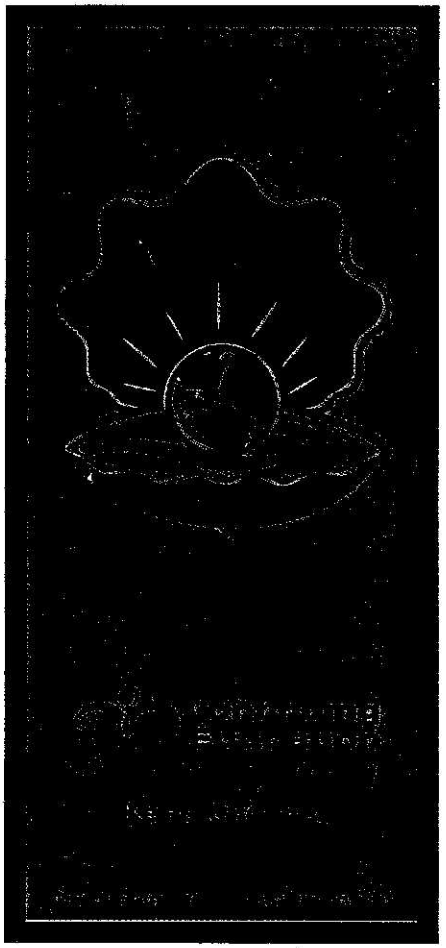

MEDICAL DISPATCH

COLD COMFORT

After decades of research, the common cold has revealed only some of its mysteries.

BY ATUL GAWANDE

There is, when you look into it, not a lot that makes sense about the common cold. For one thing, there is the name. As cold experts have pointed out, in almost all Indo-European languages one of the words or phrases for the malady plays on the word for low temperature. In Italian, the common cold is *raffreddore,* from *freddo,* meaning cold. In Hindi, the word *sardi* denotes both being made cold and a cold itself. The notion that a chill puts you at risk of catching a cold is ancient and nearly universal. Yet science has found no evidence for it. One of the first studies on the matter was led by Sir Christopher Andrewes, of the Common Cold Research Unit, in Salisbury, England, a half century ago. He and his team took a group of volunteers—half of whom had been kept warm and comfortable and half of whom had been made to take a bath, stand dripping wet without a towel in a drafty corridor for half an hour, and finally get dressed but wear wet socks for several hours—and inoculated them with cold virus up their noses. Despite a measurable drop in body temperature and considerable misery, the chilled group didn't get any more colds than the warm group. (It was work like this that earned Andrewes his knighthood.) Follow-up experiments have since demonstrated that being chilled has no effect on either the likelihood of catching a cold or the severity of a cold once you've caught it. Indeed, colds are common at every latitude and longitude in the world—in the Sahara, in Greenland, in Delhi, in Ulaanbaatar.

All the same, colds are curiously seasonal. No matter what the temperature or how subtle the change in weather, in most parts of the world the cold season begins with a peak in early fall, drones on through winter, and peaks again in mid-spring. In summer, whether it's July in Vladivostok or January in Canberra, colds almost disappear. All of this raises a basic question: How do you catch a cold, anyway?

As the Canadian cold historian J. Barnard Gilmore points out in his 1998 book "In Cold Pursuit," some of the most provocative reports on the subject have come from small, isolated communities—island villages, nuclear submarines, rural trading posts. Among these is a 1931 field study of Longyear City, an Arctic coal-mining settlement on the island of Spitsbergen, midway between the Norwegian mainland and the North Pole. For seven to nine months of the year, the town's five hundred residents were iced in, and during that time colds were almost nonexistent. Legend had it, however, that the arrival in port of the first ship of summer invariably brought with it a full-blown cold epidemic. J. Harlan Paul, a physician, and H. L. Freese, a microbiologist, decided to go to Longyear City to investigate.

The two scientists arrived in September, 1930, and spent eleven months on Spitsbergen. They found, as expected, that colds died out soon after the last boat of the year departed. The long winter that followed was quiet. Then, in May, the ice began to melt and break up. And on May 23rd, at 9 P.M., the first steamer of the 1931 season arrived in port with mail and fifty new workers for the mine. The researchers made sure they boarded the steamer while it was still out in the fjord and before anyone had disembarked. They examined each of the passengers carefully. None had any signs of a cold. A new worker was evidently in an early stage of infection; within a few hours of leaving the ship he developed symptoms of a cold.

Less than forty-eight hours later, three townspeople developed new colds. One was a storekeeper, another

an outdoor worker, and the third a miner. Paul and Freese retraced everyone's steps. They found that only the first two victims had come into close contact with any of the new arrivals. More puzzlingly, they reported, "We were unable to trace any direct contact between the man with a 'cold' who had arrived on the first boat and these three men."

Nevertheless, from that point the illness spread swiftly. Within a week, eighty-four people had come down with colds. One week later, about a hundred more caught the bug. By the end of the first month, three-quarters of the winter residents had been afflicted. Yet the researchers also discovered that there was a small but apparently hardy group of people who, despite frequent exposure, never developed the cold. A virus had travelled through town, Paul and Freese concluded, but they could not explain how.

Scientists were surprised at how difficult it is to catch a cold from a kiss.

American adults suffer an average of between two and four colds a year, and children six to eight. Although even scientists sometimes talk of "the cold virus," there is no one virus that causes colds. Since the nineteen-fifties, five families of viruses have been known to cause colds, including the coronaviruses, the parainfluenza viruses, and the adenoviruses. The most common and familiar of these is the rhinovirus family, which accounts for around forty per cent of colds and itself breaks down into at least a hundred genetically distinct viruses. The cause of approximately a third of all colds remains unknown.

Once any of these viruses get to the lining of your nose and start an infection, the miseries are pretty much the same. Symptoms usually begin from between eight and twenty-four hours after infection (though some viruses may incubate for as long as five days). On the first day of illness, you typically notice that your throat is sore or scratchy. On the second and third days, the membranes of your nose and sinuses thicken to the point of obstruction. A thin, clear secretion (made up primarily of mucoid proteins and water, but also of sloughed cells and large concentrations of virus) flows freely from the nasal lining. Inflammatory molecules in the fluid irritate the edges of your nostrils, turning them raw and red. As the cold persists, the secretions become dense and gluey. Then, after four or five days, the passages begin to open up again. For about a third of cold sufferers, a cough—caused by persistent inflammation in the upper airway—becomes the longest-lasting and most annoying problem. As a rule, cold symptoms usually go away in about a week, though for about a quarter of victims it may take two.

Antibodies from previous exposure can protect you from a particular cold-virus strain, but repeat infections are not at all uncommon. And, with so many different strains of virus circulating, you are usually an open target. Under ordinary conditions, introduction of a single rhinovirus case into the home will lead within a few days to infection in one-quarter to three-quarters of the other household members. It need not be just one virus, either. A study of Seattle families found as many as four viruses infecting a family at once.

Figuring out precisely how cold viruses pass between people has been particularly vexing. Researchers at the time of the First World War were able to demonstrate what now seems obvious: you can induce a cold by taking a concentrate from the nasal secretions of someone who has an active cold and placing it directly into either the nose or the eyes of a healthy

MICHAEL ROBERTS

person. (The virus placed in the eye runs down into the nose via the tear ducts.) Curiously, although the technique has been perfected over the decades, even direct inoculation with purified virus doesn't uniformly succeed. A few people—under ten per cent—do not get infected, despite having no antibody to the virus. Furthermore, according to nasal specimens and antibody tests, about one out of four people will develop an active viral infection yet have no symptoms of a cold—the so-called silent cold. Biopsy studies have now shown that cold viruses generally infect only a tiny portion of the nose and do very little damage by themselves. Rather, it's the inflammatory response—the attack on the virus by white blood cells and antibodies—that causes the miserable swelling and secretions. For whatever reason, there are people who, at least some of the time, manage to rid themselves of an infection without mounting this response. They can be floridly infected, shed large amounts of virus, and pass the bug on to other people, but continue to feel fine themselves.

In the nineteen-forties, high-speed flash photographs demonstrated that an ordinary sneeze expels particles like a 12-gauge spraying bird shot—sending out droplets by the thousand from the mouth and nose at velocities approaching a hundred miles an hour. A British study published in *The Lancet* showed that a culture plate placed three feet from a sneezing subject would collect more than nineteen thousand bacterial colonies. Droplets could float for minutes, and smaller particles a few microns in diameter could hover in the air for days. The conclusion that colds were transmitted by air was taken as more or less self-evident. Proving it was another matter.

In the summer of 1950, Sir Christopher Andrewes conducted a series of experiments re-creating the isolation of Spitsbergen. He assembled a dozen volunteers and deposited them in a group of houses provided by the Duke of Sutherland, on the otherwise uninhabited island of Eilean nan Ron, off the northern coast of Scotland. After the volunteers were sequestered for ten weeks, six strangers who had recently been infected with purified rhinovirus were inserted into the group. The entrance of these "invaders" was carefully scripted. First, they spent three hours in an empty room in one of the houses, making sure they were "liberal in the way they disseminated nasal discharge," as Sir Christopher later wrote. Half an hour after they left, four of the island dwellers, designated Party A in his report, were brought in to occupy the contaminated room. The invaders then entered a second room. Here Party B was present but was separated from them by a blanket that had been stretched across the room, with space above and below to allow air to pass freely. The two groups shared the room for several hours. Testing demonstrated that fine droplets from the infected group had indeed travelled throughout the room. Finally, the invaders went to a separate house, where they lived and ate with another group, Party C, for three days, providing maximum exposure. The subjects were then closely monitored for colds over the next few days. To everyone's surprise, no one in any of the parties developed a cold. Later studies attempting to demonstrate the transmission of virus through the air were hardly more successful.

In 1984, researchers at the University of Wisconsin at Madison reported the results of their own odd series of experiments. In the first set, volunteers were infected with rhinovirus, and when they were at the peak of their colds and shedding large quantities of virus they were seated at a table in a tiny, unventilated room, three feet from healthy subjects. The researchers had everyone talk, sneeze, and, weirdly, sing during the next few hours. The result? Nine sub-

THE PROMOTION

I was a dog in my former life, a very good
dog, and, thus, I was promoted to a human being.
I liked being a dog. I worked for a poor farmer,
guarding and herding his sheep. Wolves and coyotes
tried to get past me almost every night, and not
once did I lose a sheep. The farmer rewarded me
with good food, food from his table. He may have
been poor, but he ate well. And his children
played with me, when they weren't in school or
working in the field. I had all the love any dog
could hope for. When I got old, they got a new
dog, and I trained him in the tricks of the trade.
He quickly learned, and the farmer brought me into
the house to live with the family. I brought the farmer
his slippers in the morning, as he was getting
old, too. I was dying slowly, a little bit at a
time. The farmer knew this and would bring the
new dog in to visit me from time to time. The
new dog would entertain me with his flips and
flops and nuzzles. And then one morning I just
didn't get up. They gave me a fine burial down
by the stream under a shade tree. That was the
end of my being a dog. Sometimes I miss it so
I sit by the window and cry. I live in a high-rise
that looks out at a bunch of other high-rises.
At my job I work in a cubicle and barely speak
to anyone all day. This is my reward for being
a good dog. The human wolves don't even see me.
They fear me not.

—*James Tate*

jects were exposed; none came down with colds.

The researchers went on to conduct what became their best-known experiment. This time, they had their infected volunteers kiss the healthy test subjects, assuming that this would transmit the virus easily. Each subject was kissed on the mouth for a minimum of one minute. (Beyond this, the precise mechanics were not specified. "The donors and recipients were instructed to use the kissing technique most natural for them," the researchers reported.) The cold sufferers kissed sixteen subjects in all. The result was just one confirmed case of rhinovirus infection.

When they were sent home to their families, however, the experimentally inoculated people spread their colds easily and widely. The conclusion scientists drew was that a sneeze or a cough or a kiss might theoretically be capable of transmitting a cold, but it did so only rarely, and a brief exposure seemed unlikely to succeed. Some other mechanism was presumed to be more important, and this was how attention shifted to nose-wiping.

In a rather suggestive experiment, Sir Christopher's research team set up on a person's nose an apparatus with a thin tube that trickled out a clear fluid at the same rate a cold would. This fluid, however, contained an invisible fluorescent dye. With the device in place, the volunteer spent a few hours socializing with a group of people in a room—eating, chatting, playing cards. At the end, the experimenters turned out the lights and used an ultraviolet lamp to illuminate the dye. To their horror, the dye had gone everywhere—all over the person's face and hands, onto his food, onto the playing cards, onto other people's hands, and even around *their* noses. As an American observational study of an audience at a medical conference later found, in ordinary circumstances one in three adults picks his nose every hour. People rub their eyes even more frequently.

The hands had to be the culprit, and a team of scientists at the University of Virginia—Jack Gwaltney, Owen Hendley, and Richard Wenzel—provided the first persuasive evidence of this. In 1973, the team reported in the *New England Journal of Medicine* a set of studies which established a convincing chain of causation. The researchers examined ten subjects who had active colds and readily found that four had virus on their hands. When drops of extracts from their mucus were permitted to dry on nylon, wool, silk, Formica, stainless steel, wood, and other surfaces, live virus could still be recovered three hours later. This was true of virus placed on skin, too. (The virus survived well on most nonporous surfaces but hardly at all on facial tissue or cotton handkerchiefs.) If volunteers touched the contaminated surfaces—including other people's hands—the virus was picked up at least sixty per cent of the time. In another test, volunteers were asked to

touch a contaminated plastic surface with a finger and immediately either rub their eyes or put their fingers up their noses. Four out of the eleven became infected. In a follow-up study, healthy volunteers were told to rub their eyes and probe their noses after holding coffee cups that had been handled by cold sufferers who had just wiped their own noses. Fifty per cent developed colds.

And so, it was concluded, contact with your hands is how a cold virus gets passed around. It need not involve direct contact with people who have a cold. Hence the familiar advice that the best way to avoid a cold is to wash your hands frequently and not touch people with colds, especially children. That's hard to put into practice, though. When Jack Gwaltney—who has now done close to forty years of research on the common cold and is recognized as the world's foremost expert on it—is asked what he does to reduce his exposure in the cold season, he says it's pretty much hopeless. "I tried to be careful about washing my hands when my grandchildren were little, especially when they had those two ropes of mucus coming down," he recalls. "But you were still going to pick them up and hug them, and they were still going to go around touching everything. There's no avoiding it."

When he feels himself coming down with a cold, Gwaltney takes ibuprofen and an antihistamine for the next week. These won't stop a cold, but they are among the few interventions reliably proven to alleviate symptoms. The ibuprofen reduces coughing and the antihistamine reduces obstruction and runniness—although you have to take an older antihistamine, like chlorpheniramine (Chlor-Trimeton) or clemastine (Tavist), the kind that you buy over the counter and that makes you drowsy. The new ones, like Allegra and Claritin, are too narrow in their effects to work for colds. Petrolatum-based ointments are thought to protect the nostrils against the inflammatory drizzle if they're used when symptoms begin, but there are no reliable studies to prove it. What about zinc? The only consistent effect that well-designed trials have reported is that it tastes bad. Antibiotics? No benefit. Vitamin C? It won't prevent colds, according to dozens of studies, but at high doses it may reduce symptoms modestly (though not as much as an antihistamine). Echinacea? Inadequately tested. How about drinking lots of fluids, as doctors always tell you to do? There's no basis for it. As one cold researcher put it, "I'm not sure it even makes sense."

Some drugs in the research pipeline have been gathering attention of late. A new group, known as capsid-binding agents, are designed to attach to rhinoviruses and, among other things, stop them from fastening to the cells of your nasal membranes. One of these compounds recently made headlines when two randomized trials with more than two thousand patients showed that it could reduce both the severity and the duration of a rhinovirus cold. Another new group of drugs to emerge, the 3C protease inhibitors, are designed to block replication of rhinoviruses once they've penetrated your nasal cells. There have been promising preliminary results in clinical trials of one such agent, which has now been given the unpronounceable name ruprintrivir. (Manufacturers like to give drugs unpronounceable generic names because then the only thing you'll remember is whatever brand name they eventually choose.) So far, the measurable effect of each of these drugs has been modest—perhaps reducing the duration of a weeklong cold by a day or two. Even if they come to market, they will work only for a subset of cold viruses and will have to be obtained through a doctor and started no later than the first day of a cold. They're also bound to be expensive. It seems likely that a cure for the common cold will remain elusive.

We may have better luck stopping colds from spreading in the first place. At a recent scientific conference, Ronald Turner, formerly of the Medical University of South Carolina, announced the results of testing antiseptic skin cleansers that contained pyroglutamic acid or salicylic acid. Unlike most soaps, these cleansers not only killed cold viruses on people's hands immediately but continued to do so for hours afterward. Despite having their hands intentionally contaminated with rhinovirus and being made to probe their nostrils and rub their eyes, volunteers who had earlier washed with solutions containing one of the compounds developed fewer colds than those who

used a control solution. As it turns out, pyroglutamic acid is a common ingredient in ordinary skin moisturizers, and salicylic acid is used in over-the-counter acne treatments. An effective antiviral lotion may already be on the shelves.

Will these cleansers stop viruses in the real world, though? One would think so, given all the studies about hand-spread colds. Yet there always seems to be at least one study that doesn't quite square with whatever tidy theories the scientists concoct. When it comes to colds, that study is the Wisconsin poker experiment, conducted almost twenty years ago. The cold researchers at the University of Wisconsin surmised that if the main route by which colds were spread was from hand to hand (or object to hand) and then from hand to nose or eyes, preventing people from touching their noses and eyes should stop virtually all colds. So they devised a simple but clever experiment. They took healthy volunteers and volunteers who had laboratory-induced colds and put them in a room to play a marathon session of poker from eight in the morning until eleven at night. Half of the healthy subjects were allowed to play cards normally, and the other half were restrained by devices that were designed to prevent them from touching any part of their own heads or faces as they played. Some of them wore a three-foot-wide clear plastic collar; others wore an orthopedic brace that kept their arms from bending more than forty degrees. The devices were removed only for meals and trips to the bathroom. At those times, the subjects' hands were disinfected and gloved the way a surgeon's hands would be for an operation. (Assistants were provided in the event that nose-scratching was needed.) Subjects were closely monitored for the subsequent development of colds.

The results still confound cold experts. More than half of the restrained volunteers developed colds afterward—just as many as among the unrestrained volunteers. Tests confirmed that in all cases they had caught the same virus that the sick volunteers were carrying. The scientists could not say how.

There is something almost beautifully crafty about the common cold. It knows us better than we know ourselves—living and travelling and multiplying by means of an unnoticed touch, a quick, involuntary wipe of an eye, or perhaps some tic we have not yet recognized. As every textbook that addresses the subject is forced at some point to say, "Other factors may be involved." Nonetheless, there are a few things that can be said with certainty: May will come, colds will subside, and no one will know why. ♦

"And this is your father's first girlfriend, just before she was stoned to death."