CHAPTER ONE

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Losing the War on AIDS

BY ANY MEASURE, the war on AIDS has been a colossal failure. In the twelve years since the Human Immunodeficiency Virus (HIV) was announced to be the cause of AIDS (Acquired Immune Deficiency Syndrome), our leading scientists and policymakers cannot demonstrate that their efforts have saved a single life. This dismal picture applies as much to the United States as to Europe and Africa.

This war has been fought in the name of the virus-AIDS hypothesis, which holds that HIV, the AIDS virus, is a *new* cause of thirty old diseases, including Kaposi's sarcoma, tuberculosis, dementia, pneumonia, weight loss, diarrhea, leukemia, and twenty-three others (see chapter 6). If any of these previously known diseases now occurs in a patient who has antibodies against HIV (but rarely ever any HIV), then his or her disease is diagnosed as AIDS and is blamed on HIV. If the same disease occurs in a patient without HIV-antibodies, his or her disease is diagnosed by its old name and blamed on conventional chemical or microbial causes. The following examples illustrate this point:

1. Kaposi's sarcoma + HIV-antibody = AIDS
   Kaposi's sarcoma – HIV-antibody = Kaposi's sarcoma

2. Tuberculosis + HIV-antibody = AIDS
   Tuberculosis – HIV-antibody = Tuberculosis

3. Dementia + HIV-antibody = AIDS
   Dementia – HIV-antibody = Dementia

No scientist or doctor has stepped forward to claim credit for discovering a vaccine to prevent AIDS nor is any vaccine expected for several more years, at a minimum. In contrast, the post–World War II polio epidemic was declared ended in little more than a decade once the vaccines of Jonas Salk and Albert Sabin became widely available. Nor have any useful drugs to treat AIDS been produced. AIDS patients can only choose Zidovudine (AZT) or, in certain cases, dideoxyinosine (ddI) or dideoxycytidine (ddC). All these drugs were originally developed for chemotherapy to kill human cancer cells, and they bring with them all the usual effects: hair loss, muscle degeneration, anemia, nausea, and vomiting—a severe price for questionable benefits. Indeed, these drugs appear to cause AIDS-like symptoms on their own. Physicians can do little more than comfort the dying patient, monitor his condition, and hope for the best.

Public health officials still cannot show that their efforts have curbed the epidemic or that they have stopped anyone from contracting AIDS. Despite various preventive educational programs in schools and in the community at large, as well as various official and unofficial efforts to distribute condoms or sterile hypodermic needles in Europe and the United States, no actual decrease in the number of new AIDS cases can be seen anywhere. On the contrary, each year brings a greater number of new AIDS patients. Perhaps more astoundingly, even the screening of the nation's blood supply has not led to any noticeable reduction in AIDS-defining diseases (including pneumonia, candidiasis, and lymphoma) nor in death rates among blood transfusion recipients, including hemophiliacs.[1]

Worse yet, the experts have found their estimates and projections of the epidemic to be embarrassingly inaccurate. The so-called

latency period—the time between when a person is infected with HIV and develops clinical AIDS—was originally calculated in 1984 to be ten months.[2] Almost every year since, this incubation period has been revised upward. Now it is placed at ten years or longer. Even at the clinical level, doctors find the prognosis of any single infected patient frustratingly unpredictable. They cannot anticipate when a healthy HIV-infected person will become sick and which disease will affect him—a yeast infection, a pneumonia, a cancer of the blood, dementia—or perhaps no sickness at all.

Estimating the spread of the virus has meanwhile led to another problem: Officials have continually predicted the explosion of AIDS into the general population through sexual transmission of HIV, striking males and females equally, as well as homosexuals and heterosexuals, to be followed by a corresponding increase in the rate of death. However, despite the extensive use of the test for HIV antibodies—commonly known as the *AIDS test*—which first led officials to announce that 1 million Americans were already infected with the virus as of 1985, the number of HIV-positive Americans now is the same as that in 1985—1 million.[3] In short, the alleged viral disease does not seem to be spreading from the 1 million HIV-positive Americans to the remaining 250 million. AIDS itself has not yet affected larger numbers of women nor has it entered the heterosexual population outside of drug addicts: Nine of every ten AIDS patients is still male, and more than 95 percent still fall into the same risk categories—homosexuals, heroin addicts, or, in a few cases, hemophiliacs.[4] In Africa, the six million to eight million people who were said to be infected for more than a decade have translated into a mere 250,000 AIDS victims, some 3 percent to 4 percent of the HIV-positive people. The Caribbean nation of Haiti, where 6 percent of the population was known to be infected with HIV by 1985, has meanwhile remained relatively untouched by the AIDS epidemic.[5]

Something is very wrong with this picture. How could the largest and most sophisticated scientific establishment in history have failed so miserably in saving lives and even in forecasting the epidemic's toll? Certainly not for lack of resources. With an

annual federal AIDS budget now more than $7 billion, AIDS has become the best-funded epidemic of all time. Not only are tens of thousands of scientists employed in a permanent, round-the-clock race to unravel the syndrome's mysteries, but the researchers have access to the most sensitive medical technology in history. With these techniques, researchers now have achieved the ability to detect and manipulate individual molecules, an ability unimaginable to the scientists who fought smallpox, tuberculosis, and polio just years earlier. Nor have AIDS researchers suffered any lack of scientific data. With more than one hundred thousand papers having already been published on this one syndrome, literature on AIDS has been surpassed only by the combined literature on all cancers generated throughout this century.

The ultimate test of any medical hypothesis lies in the public health benefits it generates; but the virus-AIDS hypothesis has produced none. Faced with this medical debacle, scientists should re-open a simple but most essential question: What causes AIDS?

The answers to the epidemic do not lie in increased funding or efforts to make science more productive. The answers will instead be found by reinterpreting existing information. Science's most important task, much more than unearthing new data, is to make sense of the data already in hand. Without going back to check its underlying assumptions, the AIDS establishment will never make sense of its mountains of raw data. The colossal failure of the war on AIDS is a predictable consequence if scientists are operating from a fundamentally flawed assumption upon which they have built a huge artifice of mistaken ideas. The single flaw that determined the destiny of AIDS research since 1984 was the assumption that AIDS is infectious. After taking this wrong turn scientists had to make many more bad assumptions upon which they have built a huge artifice of mistaken ideas.

The only solution is to rethink the basic assumption that AIDS is infectious and is caused by HIV. But the federal and industrial downpour of funding has created an army of HIV-AIDS experts that includes scientists, journalists, and activists who cannot afford to question the direction of their crusade. Thousands

compete for a bigger slice of AIDS funding and AIDS publicity by producing ever more of the same science than the competition. In that climate, rethinking the basics could be fatal to the livelihood and prosperity of thousands.

Before becoming an HIV-AIDS advocate, John Maddox, the editor of *Nature*, the world's oldest scientific journal, described the dilemma:

> Is there a danger, in molecular biology, that the accumulation of data will get so far ahead of its assimilation into a conceptual framework that the data will eventually prove an encumbrance? Part of the trouble is that excitement of the chase leaves little room for reflection. And there are grants for producing data, but hardly any for standing back in contemplation.[6]

INFECTIOUS AIDS—DID WE MAKE THE RIGHT CHOICE?

Any new disease or epidemic forces medical experts to search for the new cause, which they hope to bring under control. From the start, however, they have a responsibility to consider both possible causes for an epidemic: (1) a contagious, infectious agent such as a microbe or a virus or (2) some noninfectious cause such as poor diet or some toxic substance present in the environment or a toxin consumed in an unusually large quantity. Lives depend on the right answer to this primary question. A contagious disease must be handled very differently from a noncontagious one. Unnecessary public hysteria, inappropriate prevention measures, and toxic therapies are the price for misidentifying a noncontagious disease for one that is contagious.

The period of research into the cause of AIDS in which both infectious and noninfectious agents were considered lasted only three years. It started with the identification of AIDS in 1981 and officially ended in April 1984 with the announcement of the "AIDS virus" at an international press conference conducted by

the secretary of Health and Human Services and the federal AIDS researcher Robert Gallo in Washington, D.C.[7]

This announcement was made prior to the publication of any scientific evidence confirming the virus theory. With this unprecedented maneuver, Gallo's discovery bypassed review by the scientific community. Science by press conference was substituted for the conventional process of scientific validation, which is based on publications in the professional literature. The "AIDS virus" became instant national dogma, and the tremendous weight of federal resources was diverted into just one race—the race to study the AIDS virus. For the National Institutes of Health (NIH), the Centers for Disease Control (CDC), the Food and Drug Administration (FDA), the National Institute on Drug Abuse (NIDA), and all other divisions of the federal Department of Health and Human Services and for all researchers who received federal grants and contracts, the search for the cause of AIDS was over. The only questions to be studied from 1984 on were how HIV causes AIDS and what could be done about it. The scientists directing this search, including Robert Gallo, David Baltimore, and Anthony Fauci, had previously risen to the top of the biomedical research establishment as experts on viruses or contagious disease. Naturally the virologists chose to employ their familiar logic and tools, rather than dropping their old habits to meet new challenges, when AIDS appeared in 1981.

But serious doubts are now surfacing about HIV, the so-called AIDS virus. Dozens of prominent scientists have been questioning the HIV hypothesis openly during the past eight years, and the controversy gains momentum with each passing week. The consensus on the virus hypothesis of AIDS is falling apart, with its advocates digging in their heels even as its opponents grow in number.

As with most diseases today in the industrial world, AIDS appears not to be a contagious syndrome. The evidence for this exists in the scientific literature, but this evidence is widely neglected by researchers intent on viewing the data through the single lens of virology. If biomedical science has erred, if AIDS is not caused by a virus, then the entire medical and public health approach to the

syndrome is misdirected. People are not being warned about the true risks for developing AIDS, doctors are using ineffective or dangerous treatments, and public fear is being exploited.

In view of the omnipotence of modern science, an error in identifying the cause of AIDS may seem inconceivable. How could a whole new generation of more than one hundred thousand AIDS experts, including medical doctors, virologists, immunologists, cancer researchers, pharmacologists, and epidemiologists—including more than half a dozen Nobel Laureates—be wrong? How could a scientific world that so freely exchanges all information from every corner of this planet have missed an alternative explanation of AIDS?

Faith in the infallibility of modern science has deep and solid roots. Rightfully, medical science is admired for its knowledge about infectious diseases and its virtuosity in dealing with them. The elimination of infectious diseases with vaccines and antibiotics has, in fact, been the most complete success story in the history of medicine. Today all infectious diseases combined cannot claim 1 percent of the lives of modern Americans and Europeans anymore.[8] Since the late nineteenth and early twentieth centuries, when Robert Koch found the tuberculosis bacillus and Walter Reed found the yellow fever virus, ever more victories have been won against infectious diseases.

These pioneers established models that every scientist confronted with an unexplained disease wants to imitate: Pick an unexplained disease, discover a causative virus or microbe and invent a curative drug or vaccine, and become a medical legend just like Koch, Pasteur, Semmelweis, and Reed. The Koch-Pasteur model set off a medical gold rush of microbe and virus hunters that came to a happy end when all major infectious diseases were apparently eliminated from the Western world, the last being polio in the 1950s.

Only noninfectious diseases like cancer, emphysema, multiple sclerosis, Alzheimer's, and osteoporosis have not yielded to medical control. On the contrary, these diseases have increased their shares as causes of death and illness, having taken the place that infectious diseases once held.

It was on the basis of this impressive record of triumphs over infectious diseases that the secretary of Health and Human Services and the virus researcher Robert Gallo promised so confidently at their international press conference in 1984 to stop the AIDS epidemic in just two years with a vaccine against the "AIDS virus."[9] Is it possible that this promise could not be kept because the hypothesis was simply wrong and that AIDS might not even be caused by a virus? Could a medical science that had broken the secrets of infectious diseases long ago have prematurely misdiagnosed AIDS as an infectious disease?

Because of their inherent potential to spread beyond control, infectious diseases are the first concern of public health officials, politicians, and taxpayers. Given the human tendency to fear the worst, the public is readily inclined to believe in infectious causes of disease. Among scientists, the infectious disease experts are the primary beneficiaries of the fear of contagion. With the argument of caution on their side, the infectious disease experts claim the privilege to convict suspect microbes without trial—while putting the burden of proof on all alternative hypotheses.

But the premature assumption of contagiousness has many times in the past obstructed free investigation for the treatment and prevention of noninfectious disease—sometimes for years, at the cost of many thousands of lives. Even when nontransmissible causes would have provided much better explanations and much easier prevention than hypothetical microbes, the microbes were pursued because antibiotics and antiviral vaccines promised proven therapies and prevention as well as professional and commercial gratification. As the research establishment becomes more centralized, bureaucratized, and fraught with commercial conflicts of interest, each episode achieves more monstrous proportions. The U.S. Department of Health and Human Services' premature endorsement of the hypothesis that AIDS is a sexually transmitted, infectious epidemic caused by the newly discovered "AIDS virus" could be the most costly and most harmful of these fatal errors in the history of medicine if AIDS proves to be not infectious.

THE SMON FIASCO

Indeed, blaming noninfectious diseases on infectious microbes has occurred many times before. Hidden in foreign-language materials and the footnotes of obscure sources lies the story of SMON, a frightening disease epidemic that struck Japan while the war on polio was accelerating in the 1950s. In many ways, SMON anticipated the later AIDS epidemic. For fifteen years the syndrome was mismanaged by the Japanese science establishment, where virtually all research efforts were controlled by virus hunters. Ignoring strong evidence to the contrary, researchers continued to assume the syndrome was contagious and searched for one virus after another. Year after year the epidemic grew, despite public health measures to prevent the spread of an infectious agent. And in the end, medical doctors were forced to admit that their treatment had actually caused SMON in the first place.[10]

Once the truth about SMON could no longer be ignored, the episode dissolved into lawsuits for the thousands of remaining victims. This story has remained untold outside of Japan, ignored as being too embarrassing for the virus hunters. It deserves to be told in full here.

The patient was middle aged, suffering from a mysterious nerve disorder that had already paralyzed both her legs. Reisaku Kono was there to observe the victim because of his work studying poliovirus, which in a few infected individuals would break into the central nervous system, causing progressive paralysis and sometimes a slow, miserable, death. While the condition he examined that day in 1959 was not polio, it bore a certain resemblance to it. And the suspicion was growing that this, too, could be the result of some undiscovered virus, perhaps one similar to poliovirus.

Kono was visiting the patient at the hospital affiliated with Mie University's medical school. Hiroshi Takasaki, a professor of medicine at the university, told Kono about a number of these cases he had recently seen at the hospital. They now realized they were facing an outbreak of something new, not just a minor mystery that

doctors would catalog and forget. Just the previous year, medical Professor Kenzo Kusui had published a report of another such case in central Japan: The patient had suffered a similarly strange combination of intestinal problems, manifesting as internal bleeding and diarrhea, with symptoms of nerve degeneration. This illness, stomach pains or diarrhea followed by nerve damage, had been noticed in a few isolated cases as early as 1955, but was now turning into a local epidemic.

More published reports began accumulating after Kono's visit to the hospital. The next five years saw seven major regional epidemics of the new polio-like syndrome, with the annual number of new cases increasing from several dozen in 1959 to 161 victims by 1964—an alarming rate for those small areas. Scientists jumped to conclusions, believing they had every reason to assume the disease was infectious. Just its sudden appearance was enough evidence to convince them. The disease also broke out in clusters around specific towns or cities, and clusters were seen within families. The first person to develop the condition in each of these families was followed by a relative within several weeks. Many outbreaks were centered around hospitals, places notorious for spreading disease. The annual peak of new patients occurred in late summer, hinting at possible spread of the disease through insects. Those scientists who first thought the disease might be related to some noncontagious occupational hazard were quickly dissuaded once the data showed that the disease lacked the expected preferences. Farmers, for example, who would be more easily exposed to pesticides, had a lower-than-average incidence. Medical workers, on the other hand, had a rather high rate of this condition—further suggesting it was contagious.

However, the scientists investigating the epidemic did notice some important contradictions. For instance, the disease had an odd, amazingly consistent bias for striking middle-aged women, but was less common among men and could hardly be found among children, who normally transmit virtually any infectious disease. Careful medical inspection showed that the symptoms did not coincide with those typically expected for an infection. Blood

and other bodily fluids, which usually circulate a virus throughout the body, showed no abnormalities, nor did the patients manifest any fevers, rashes, or other signs of fighting off some invading germ. These important pieces of evidence should have raised doubts about the viral hypothesis.

The virus hunt pressed onward. Scientists were expecting to find a virus that primarily induced diarrhea, as was the case in polio. Looking back on this period, Kono has since become admirably frank about his early biases, shared at the time by his fellow virologists: "I was at that time engaged in poliovirus research, so I suspected such a virus to be the cause."[11] Despite years spent searching for the elusive virus, he never could isolate a single one from any patient. Kono patiently reported his null results as he plodded forward.

Meanwhile the epidemic was growing and the 1964 Olympic Games were approaching. Ninety-six new cases had been diagnosed the previous year, and the increased number of cases was being accompanied by new symptoms. Some victims, for example, were now suffering debilitating blindness. Preparing to host tourists from around the world for the 1964 Olympics, Japan could ill afford to have an uncontrolled plague. To make matters worse, forty-six new patients suddenly appeared around the city of Toda, one of the locations for Olympic events. Embarrassingly dubbed the "Toda disease," this outbreak directly threatened Japan's reputation and tourist industry while focusing public fear on the epidemic. Etsuro Totsuka, later to become a lawyer for victims of the disease, summarized the public mood at the time: "Even I was quite worried at the time, as a university student studying physics. The general public, including me, was extremely worried; we didn't know how to prevent it, and there was no cure."[12]

In May of 1964, at the 61st General Meeting of the Japanese Society of Internal Medicine, the disease was raised as a formal topic. Kenzo Kusui, one of the first doctors to report patients stricken with this condition, chaired that session. The participating researchers gave the disease a formal name, *Subacute Myelo-Optico-Neuropathy* (SMON), and they agreed on a standardized

clinical diagnosis. The Japanese Ministry of Health and Welfare quickly provided a research grant and launched a formal commission to investigate the epidemic under the leadership of Magojiro Maekawa, a medical professor at Kyoto University. Kono was one of several virologists named to the commission, thereby establishing its mandate as a formal search for a virus.

The same year brought the first sign of a possible breakthrough. Masahisa Shingu, a virologist at Kurume University and a fellow member of the commission, announced his discovery of a virus in excretions from SMON patients. The virus was classified as an *echovirus*—an acronym for enteric cytopathogenic human orphan virus. The viruses were called *orphans* because they had been discovered accidentally during polio research but caused no disease. Echoviruses were known for infecting the stomach or intestines, and Shingu found evidence of infection in various SMON sufferers. He excitedly drew the conclusion that this orphan virus had finally been matched with a disease. Perhaps, he speculated, this virus could also occasionally break into the nervous system, much like poliovirus. He published the finding in 1965, unabashedly boasting he had isolated the syndrome's cause.

But Kono, knowing the potentially disastrous results of blaming the wrong microbe for the disease, took a more cautious attitude. In 1967, after three years of research trying to confirm Shingu's claims, Kono could only report to a SMON symposium that he had not isolated the virus from patients, nor could he find even indirect evidence that the patients had previously been infected. Kono's better judgment saved Japanese science from stampeding in the wrong direction. He was fully vindicated four years later when other researchers announced the same lack of evidence to suggest any danger from Shingu's virus.

In the midst of this fruitless investigation, the Maekawa team made a surprising observation that was tragically brushed aside. According to surveys of hospitals, about half the SMON patients had previously been prescribed a diarrhea-fighting drug known by the brand name Entero-vioform, and the other half had received a compound marketed under the name Emaform. Both drugs were

prescribed for problems of the digestive tract—the early symptom of SMON. The suspicion naturally arose that these drugs might play some role in the syndrome, but the commission, intent on the viral hypothesis, bowed to the consensus view of SMON as contagious and quickly dismissed this, noting that two different drugs should not cause the same new disease. Had the commission researchers checked further, however, they would have discovered that the two drugs were merely different brand names applied to the same drug, a fact that did not surface for several years.

The SMON commission dissolved in 1967, a failure. The cumulative total of reported SMON cases had meanwhile reached nearly two thousand by the end of 1966, a significant but not terrifying number. If not for the quiet growth of the disease epidemic, the floundering virus hunt might have killed public interest in SMON research altogether.

Almost immediately after the official commission was dissolved, two rural areas in the Okayama province began reeling from a new explosive outbreak of the syndrome. Dozens of elderly women, and some men in their thirties, began filling the nearby hospitals, totaling almost 3 percent of the local population by 1971. Scientific attention was again focused on SMON, with the specter of a resurgent epidemic recharging the virus hunt.

Two researchers issued reports in 1968 describing a new virus found in tissues of SMON patients, stirring a wave of excitement. The agent fell under the classification of "Coxsackie" viruses, a type of passenger virus known to infect the digestive tract and originally discovered as a by-product of polio research. It was another false alarm: The virus proved to be an accidental laboratory contamination.

In 1969 the Japanese Ministry of Health and Welfare, anxious about the expanding epidemic, again decided to form an official investigating body. With more than ten times the funding of the old 1964 commission, the SMON Research Commission became the largest Japanese research program ever devoted to a single disease. Its first meeting was held in the heavily affected Okayama province in early September. The consensus view among Japanese

scientists had completely focused on some unknown virus as the probable cause of the disease. The naming of Kono, Japan's most respected virologist, as chairman symbolically established the new commission's priorities.

So far, after more than a decade of persistent research, the virologists had come up painfully empty-handed. Kono, though himself a virologist, now saw the need to explore alternative hypotheses. Kono divided the commission's work into four sections, each led by top Japanese medical officials. An epidemiologist was put in charge of a group conducting nationwide surveys on the extent, distribution, and associated risk factors of the disease. Kono himself headed the virology group. A pathologist headed a group focused on analyzing autopsy results, and a neurologist led a group classifying neurological and intestinal SMON symptoms. Altogether, forty top scientists participated in the commission during 1969.

Although Kono had opened the door for alternative research directions, the virus hunt accelerated—for just at this time, some key scientific claims by English and American virologists were beginning to have a profound impact on virus research worldwide, and particularly on SMON research in Japan. The first came in the early 1960s from virologist Carleton Gajdusek of the American National Institutes of Health, who reported finding evidence of the first "slow virus" in humans. (A slow virus is a virus alleged to produce a disease long after the original infection, that is, after a long "latent period." See chapter 3.) He believed it to be the cause of kuru disease among New Guinea natives. Kuru was a slowly progressing neurological disease that led to the debilitation of motor skills. The patients presented with symptoms of tremor and paralysis similar to Parkinson's disease. Gajdusek claimed to have found the kuru virus, but his methods were highly unusual by any scientific standards. He had never actually isolated a virus but instead had ground up the diseased brains of dead kuru victims and injected these unpurified mixtures into the brains of living monkeys. When some of the monkeys showed deficits in motor skills, Gajdusek published his findings in the world's oldest scientific

journal, *Nature*, and was lauded by his fellow virologists. The second alleged discovery came from London's Middlesex Hospital in 1964, directly inspired by Gajdusek's claims. Two researchers found a virus that was believed to cause the childhood cancer, Burkitt's lymphoma. It was the first virus ever claimed to cause human cancer and the first known human virus thought to have an incubation time between infection and disease measured in years, rather than days or weeks.

These claims were made by very large and respected research establishments; therefore, Kono could not afford to ignore them. Other medical experts on the SMON commission warned him that the SMON symptoms did not resemble those of standard virus infections, suggesting the condition was not contagious. Kono, however, brushed aside this advice, arguing that if scientists were unwilling to consider the possible existence of nonclassic viruses then "Dr. Gajdusek could not have established a slow virus etiology for kuru."[13] Imitating Gajdusek's methods, he injected unpurified fluids from SMON patients into the brains of experimental mice and monkeys, hoping to cause the disease and isolate the guilty virus. Frustrated, but not willing to give up, he decided the American researchers were better equipped to find such a virus. He mailed the same fluid samples directly to Gajdusek, who repeated the inoculations into the brains of his own chimpanzees; after three years, they, too, remained perfectly normal. With that, Kono finally abandoned the search for a "slow virus."

With their virus research faltering, a few of the investigators began looking for bacteria. One lab found that SMON patients had imbalanced levels of the beneficial bacteria normally growing in everyone's intestines, but it could not isolate any new invading microbe. Kono's own lab, as well as two other researchers, did notice unusually large amounts of a mycoplasma, one type of bacterial parasite, in disease victims. However, since mycoplasma are found in a large percentage of human populations and are usually known for being either relatively harmless or causing some pneumonias, Kono and his fellow researchers decided against pursuing this further.

By 1970, one fact stood out more agonizingly than any other:

Twelve years of microbe research into the SMON epidemic had yielded nothing but dead ends. Yet the pressure continued to mount as the death toll rose. The year 1969 alone claimed almost two thousand new SMON victims, the worst toll ever. Kono and his commission were running out of options.

Fortunately for the Japanese people, several researchers on the commission were not virus hunters, and these scientists actually rediscovered the evidence for a toxin-SMON hypothesis.

The Drug Connection

As the race to find a SMON virus was capturing all the attention, other scientists were turning up some important clues to the mysterious syndrome. One pharmacologist, Dr. H. Beppu, visited the hard-hit Okayama province in 1969 to investigate the increasing outbreak and independently discovered the same coincidence the Maekawa group had years earlier—that SMON victims had taken certain drugs to treat diarrhea. Unlike the Maekawa group, Beppu investigated and found that Entero-vioform and Emaform—the diarrhea-fighting drugs found present in an earlier SMON study—turned out to be different brand names for a substance known as *clioquinol*, a freely available medical drug used against some types of diarrhea and dysentery. Beppu fed the chemical to experimental mice, hoping to see nerve damage like that in SMON, but was disappointed when the mice merely died. He missed the significance of his own results. Clioquinol was sold because it was believed not to be absorbed into the body, instead remaining in the intestines to kill invading germs. The death of Beppu's animals, however, proved that the drug not only entered the body, but could kill many essential tissues in the animal. His experiment led the SMON commission to rediscover this clioquinol connection the following year. "He later confessed to feeling stupid, because he gave up the experiment when the animals died," Totsuka explained of Beppu. "He wanted to prove a neurological disorder, but only proved the drug's severe toxicity."[14]

Meanwhile the SMON commission's first priority lay in

conducting a nationwide survey of SMON cases reported since 1967, gathered by sending questionnaires to doctors and hospitals throughout Japan. In the fall of 1969, shortly after the commission began analyzing survey data, the head of the clinical symptoms section came across several SMON patients with a strange green coating on their tongues, a symptom unnoticed before nationwide data were gathered. At first other researchers on the commission suggested that this new symptom might be caused by *Pseudomonas* bacteria, which can release colorful blue and green pigments. One of the investigators did isolate such a bacterium from some patients but not from others, and the inexplicable symptom merely became a part of the revised SMON definition. The green tongue observation achieved new importance in May of 1970, when one group of doctors encountered two SMON patients with greenish urine. Enough of the pigment could be extracted to perform chemical tests. Within a short time the substance was determined to be an altered form of clioquinol, the same drug previously found by the Maekawa commission and by Beppu.

This raised two very troubling questions. Clioquinol had been marketed for years on the assumptions that it only killed amoeba in the intestinal tract and could not be absorbed into the body; its appearance on the tongue and in the urine now proved this belief wrong. Could the medicine therefore have unexpected side effects? And why would SMON patients manifest the drug by-products so much more obviously than the rest of the population? This latter question particularly bothered one neurology professor at Niigata University, Tadao Tsubaki. Making an educated guess, he openly formulated the hypothesis abandoned by earlier investigators—that SMON might be the result of clioquinol consumption, not of a virus.

As expected, the interpretation of SMON as a noncontagious syndrome did not become popular among the virus hunters. And the suggestion that clioquinol might be guilty met even stronger resistance, for the drug was being used to treat the very abdominal symptoms found in SMON. Doctors, naturally, were reluctant to believe they were exacerbating these abdominal pains and thus

adding the severe insult of nerve damage to the injury. Totsuka recalled that "doctors and scientists wanted to believe in a virus, because they prescribed clioquinol. One of the drug's main side effects was constipation and abdominal pain. Now because the drug caused pain, doctors again prescribed the drug."[15] Doctors, ignorant of clioquinol's side effects, assumed the stomach pains resulted from the primary sickness and kept increasing the dose in a vicious cycle.

Tsubaki knew he had to gather strong evidence before they could shoot down the virus-SMON hypothesis. Pulling together several associates, Tsubaki arranged for a small study of SMON patients at seven hospitals. By July of 1970 he had already compiled enough data to draw several important conclusions: 96 percent of SMON victims had definitely taken clioquinol before the disease appeared, and those with the most severe symptoms had taken the highest doses of the medication. The number of SMON cases throughout Japan, moreover, had risen and fallen with the sales of clioquinol.

This clioquinol hypothesis explained all the strangest features of the SMON syndrome, such as its preference for striking middle-aged women, its absence in children (who received fewer and smaller doses of the drug), and its symptomatic differences from typical viral infections. It also shed new light on the supposed evidence that SMON was infectious: its tendency to appear in hospital patients, to cluster in families, to afflict medical workers, and to break out more heavily in the summer—all of these reflected the patterns of clioquinol use. The epidemic itself had begun shortly after approval for pharmaceutical companies to begin manufacturing the drug in Japan.

In 1970 there were thirty-seven SMON cases in January and nearly sixty more cases during the month of July. The Japanese Ministry of Health and Welfare decided not to wait any longer, and promptly released the information about clioquinol to the press. The news of Tsubaki's research reached the public in early August, and the number of new SMON cases for that month dropped to under fifty, presumably because some doctors stopped

prescribing clioquinol to their patients. On September 8 the Japanese government banned all sales of the drug, and the total new caseload for that month sank below twenty. The following year, 1971, saw only thirty-six cases. Three more cases were reported in 1972, and one in 1973. The epidemic was over.

For the next few years, the commission's research focused on confirming the role of clioquinol. In 1975 it released a comprehensive report. Systematic epidemiological surveys matched use of the drug with outbreaks of the syndrome, and experiments were performed on animals ranging from mice to chimpanzees. As it turned out, the drug induced SMON-like symptoms most perfectly in dogs and cats. Meanwhile, the investigators began uncovering individual case reports of SMON symptoms from around the world, wherever clioquinol had been marketed. Totaling roughly one hundred cases, the published reports ranged from Argentina in the 1930s to Great Britain, Sweden, and Australia in more recent times, often with the doctor specifically pointing out the association with the use of clioquinol or similar compounds. Ciba-Geigy, the international producer of the drug, had received warnings of these incidents years before the Japanese epidemic, a fact that later became the basis of a successful lawsuit against the pharmaceutical company.

Clioquinol, often marketed under the brand name Enterovioform, has been available for decades throughout many countries in the world. But while doctors outside Japan have published a few reports of SMON-like conditions, no real epidemic of the disease has ever broken out in Europe, India, or other countries with widespread use of the drug. Much of the difference lies in the heavier consumption of clioquinol in Japan, where the stomach, rather than the heart, is considered the seat of the emotions. The general over-prescription of drugs in that country further worsens the problem, such that many SMON victims had histories of using not only clioquinol but also multiple other medications, often at the same time. Government health insurance policies have encouraged this over-medication, paying doctors for every drug prescribed to the patient. As a result, the proportion of the Japanese health

insurance budget spent on pharmaceutical drugs grew from 26 percent in 1961 to 40 percent in 1971, a level many times higher than in other nations. By the time the Japanese government decided to ban clioquinol, many of the hardest-hit SMON patients had each consumed hundreds of grams over the course of several months. And whereas the outside world mostly used clioquinol to prevent diarrhea when traveling abroad, the Japanese usually received the drug as hospital patients, having an already weakened condition.

Years later, at a 1979 conference, Reisaku Kono asked, "Why had research on the etiology of SMON not hit upon clioquinol until 1970?" The question has two answers; both pointed out by Kono himself:

> There were at least two occasions when physicians suspected that clioquinol might have something to do with SMON. I know of a certain professor rebuking one of his staff physicians for connecting clioquinol with SMON. In 1967 the study group of the National Hospitals on SMON reported as follows: Entero-vioform (clioquinol's brand name), mesaphylin, Emaform (home producer of clioquinol), chloromycetin and Ilosone were often prescribed to SMON patients, but no link was found between Entero-vioform and SMON. This report referred to Entero-vioform in particular so that clioquinol must have been suspected by someone in the study group. Dr. Tsugane, who was responsible for the survey, said that the survey was not thorough enough to unearth clioquinol as a causative agent. One of the reasons could have been that clioquinol had been used as a drug for the intestinal disorders of SMON, and it was hard to believe that clioquinol was toxic rather than a remedy.[16]

Referring here to the tentative fingering of clioquinol by the Maekawa group, Kono observed that too many medical doctors refused to recognize the possibility of an iatrogenic disease (one caused by the doctor's treatment). They understandably disliked the idea that a drug might cause some of the very symptoms for which it was prescribed in the first place.

Another, more fundamental, reason for overlooking clioquinol lay in the prevailing attitude of the virologists. As expressed by Kono, "We were still within grasp of the ghosts of Pasteur and Koch!"[17] SMON, a vaguely polio-like syndrome, had first appeared in the midst of a war against polio. The polio virologists, Kono included, were naturally inclined to search for a new virus as the cause of the new disease. The Japanese government, having funded poliovirus research, simply kept up the momentum by funding the same virologists to study SMON. Thus, the virus hunters received the lion's share of research moneys and attention, and with that the power to direct the SMON research program. Had it not been for Kono's foresight in also appointing nonvirologists to the commission, the epidemic might have lasted much longer.

At least the epidemic had ended, with the truth universally recognized. The virologists had learned their lesson, and the search for SMON viruses was over.

Or was it? Incredibly, against all evidence, the SMON virus hunt suddenly came back to life within weeks of the epidemic's end. The fight over the cause of the syndrome was to drag on for several more years, with the virus hunters simply ignoring the fact that SMON itself had disappeared after the ban on clioquinol.

The Virus Hunt Revived

In February of 1970, while the SMON Research Commission was still scrambling to find the cause of the epidemic and a few researchers were just beginning to notice the greenish pigments in some patients, Assistant Professor Shigeyuki Inoue at Kyoto University's Institute for Virus Research claimed discovery of a virus in the spinal fluid and excretions of SMON patients. He added the extracts to laboratory culture dishes of hamster tumor cells and found that the new agent killed the cells. With more experimentation, Inoue classified the microbe as a new herpes virus. He was able to isolate this particular virus from nearly all SMON patients he tested, more than forty in all, and found antibodies against the virus in other victims.

Reisaku Kono moved promptly to test these new observations. He used Inoue's own virus isolate and cell cultures, and within three months of Inoue's first report found that the virus could kill some cells. These particular cells, however, were extremely sensitive, prone to spontaneous death even in the uninfected cultures. Kono began to suspect the virus was harmless. He also could not isolate the virus from any SMON patients, unlike Inoue's lab. Perhaps, he openly wondered, the alleged virus might not exist at all.

A number of scientists sided with Kono, insisting they could neither find the virus in SMON victims nor cause cell death in culture dishes by adding virus samples from Inoue's lab. Nor could Inoue's extracts induce symptoms when injected into mice. Indeed, Kono and some of these other investigators could never even find the virus at all, reinforcing the growing question of whether it truly existed. The virus could not even be detected in the samples sent them from Inoue. An occasional mouse injected with Inoue's supposed virus would become sick, but the symptoms did not resemble those of SMON. Kono won allies among his peers when many of them could not reproduce Inoue's observations, a troubling problem for any scientific claim.

Nevertheless, Inoue had meanwhile rapidly achieved celebrity status for his "SMON virus" during 1970, before the clioquinol announcement that August. The Japanese news media had prematurely publicized his results, creating the widespread impression that the cause of SMON had been determined. Hysteria over the contagious plague swept through much of the country, causing frightened family members of SMON patients to avoid contact with their "infected" relatives, and leading many of the victims to commit suicide. "Patients were isolated, many committed suicide, and there was national panic," reflected Totsuka on the horror he witnessed. "I met families who lost relatives. I heard from most or all of my 900 clients; most of the patients said they very much feared and dreaded the disease. Everybody told me about that, about those sufferings. Once they found out about the drug, they were somewhat relieved, because it was not infectious."[18]

The new virus-SMON hypothesis had indeed achieved a life of its

own, causing a few scientists to jump on the Inoue bandwagon; months *after* clioquinol had been banned and the epidemic had virtually disappeared, several labs excitedly issued reports claiming they could reproduce Inoue's findings. Inoue himself further insisted he had caused SMON-like symptoms in mice—including weight loss, paralysis, and nerve damage—either by injecting the virus into their brains or feeding the virus to other immune-suppressed mice unable to fight off the infection. Inoue and a collaborating scientist also both claimed to have photographed the virus directly with electron microscopes, although Inoue's colleague eventually retracted his own report as having been mistaken.

A meeting of the SMON Research Commission was finally held in July of 1972 to resolve the controversy. Until that time, Inoue's results had received attention and concern equal to the clioquinol research. But based on the inability of many scientists to produce the same results, which must be done for any scientific hypothesis to be accepted, the members at the meeting decided not to focus any more research efforts on the Inoue virus. Samples were frozen for future study, and the group thereafter devoted its resources to studying clioquinol.

Despite the absence of confirming evidence, and despite the disappearance of SMON following the ban on clioquinol, Inoue and his supporting colleagues continued to publish reports of evidence for the virus hypothesis. This publicity carried the Inoue hypothesis overseas, leading the 1974 edition of the *Review of Medical Microbiology*, an American textbook, to incorporate the Inoue virus hypothesis of SMON.

Shocked and angered by the favorable publicity surrounding Inoue's hypothesis, Kono wrote a letter to the British medical journal *Lancet*; the letter was published in August of 1975. The international popularity of virus research had whetted scientists' appetite for Inoue's hypothesis, but Kono also knew he was battling a nearly complete ignorance of the SMON episode outside Japan:

> Inoue et al. published several papers on SMON virus, and a standard textbook adopted Inoue's virus theory as

> confirmed. However, research in the laboratories of the SMON Research Commission in Japan failed to confirm Inoue's results. Unfortunately, this negative information has not been published in English.[19]

The epidemic's toll had officially ended in 1973 with 11,007 victims, including thousands of fatalities. Angered upon learning of Ciba-Geigy's disregard of previously reported clioquinol toxicity, many of these patients filed a lawsuit in May of 1971 against the Japanese government, Ciba-Geigy of Japan, fifteen other distributors of the drug, and twenty-three doctors and hospitals. The ranks of the plaintiffs soon swelled to some forty-five hundred, with legal action initiated in twenty-three Japanese district courts. The largest group of SMON victims sued jointly in the Tokyo District Court. When frustrations mounted over the slow and indecisive actions of their lawyers, nine hundred of the plaintiffs broke away to form a second group. The aggressive investigations conducted by this new legal team reinvigorated the case, bolstering the positions of the plaintiffs in parallel lawsuits. Etsuro Totsuka, one of the thirty members of this legal team, has described the fight:

> We were the only team gathering information outside Japan, inviting foreign experts to testify in Japanese courts, discovering the United States FDA had restricted clioquinol ten years before Japan, and waging an international campaign against Ciba-Geigy...
>
> We found many foreign doctors who had reported clioquinol side effects before. They were contacted by Ciba-Geigy, and except in one or two instances were persuaded not to help us. By the time I saw the doctors, they had already been contacted by the other side. They had been invited on trips, some to Ciba-Geigy's headquarters... We felt they were already compensated, under the condition not to tell us anything.[20]

The two sides slugged it out for several years, but the testimony by members of Kono's SMON Research Commission proved devastating, and a string of legal victories followed in the courts.

Today most scientists and laymen outside Japan have never heard of the virus-SMON controversy, even in the face of the lawsuit against the distributors of clioquinol, television documentaries in Germany and England on clioquinol, and two conferences during the 1970s on iatrogenic (medically caused) disease. The story that SMON research had ignored the evidence of a toxic cause for fifteen years and had sacrificed thousands of human lives to a flawed virus hypothesis is too embarrassing to the virus-hunting establishment to record.

AIDS: AN ENCORE OF THE SMON DISASTER?

When Michael Gottlieb, at the medical center of the University of California, Los Angeles, observed five patients dying from bizarre diseases during the early months of 1981, he already suspected he was opening the curtain on a new epidemic. AIDS, like SMON, did grow dramatically over the next decade, although not explosively as other new, infectious epidemics, like a seasonal flu or cholera epidemic did before the days of antibiotics. AIDS appeared with unnerving suddenness in major cities of the United States and Europe—as well as in Africa and the Caribbean, where mystique-ridden stereotypes of these countries lent credibility to stories of widespread devastation.

Again following the pattern of SMON, AIDS circumstantially appeared to be contagious, with cases turning up among hemophiliacs and other recipients of blood transfusions and with outbreaks of the syndrome found among mutual sex partners in the homosexual community. In other words, potential transmission routes for some unknown virus could be identified. But other evidence actually indicated both syndromes to be noninfectious: Whereas SMON struck middle-aged women more than any other group, AIDS showed an extreme bias for young men in their twenties to their forties, mostly heroin addicts and homosexuals.

SMON, as it turned out, resulted from the use of a prescription drug for the early symptoms of SMON itself, a fact so horrifying to doctors that the possibility was repeatedly cast aside whenever

the evidence would emerge. AIDS may also be partly the product of a prescription medicine—AZT, the very one provided as a therapy for AIDS. Once again, that horrifying possibility is cast aside by scientists and doctors.

AIDS, too, became a centrally managed epidemic, with the U.S. National Institutes of Health directing most research and preventive education in this country. Special commissions were also set up by prestigious scientists and government officials, beginning in 1986, to focus all resources and efforts into a concerted war on AIDS.

And from literally the first week after Gottlieb reported his AIDS cases, the virus hunters began the search for an AIDS virus, dominating the research effort just as their Japanese counterparts had done with SMON. Once again, several viruses in turn were blamed, from the herpes-type cytomegalovirus to the retrovirus HTLV-I, until a consensus formed around another retrovirus, the Human Immunodeficiency Virus (HIV).

The SMON epidemic finally ended because Reisaku Kono and other Japanese scientists possessed the wisdom to direct some resources into nonvirological research and listen when those other investigators found answers. But the officials and scientists driving our war on AIDS have had little tolerance for alternatives. Ignoring the lessons of SMON and other diseases, today's biomedical research establishment blocks virtually all research and questions that disagree with the consensus view of infectious AIDS.

If the war on SMON was a molehill of misdirected science, AIDS has become an unmovable mountain. The difference lies in the respective sizes of the scientific establishments involved. Not only is the funding for AIDS research much greater than the amount spent on SMON, but the preexisting structure—measured in number of scientists, size of departments, and sheer volume of published data—now far exceeds the combined size of all scientific endeavors in human history. Thus, errors necessarily become magnified beyond any individual's control, and adjustments to AIDS theory become ever more difficult to change.

SMON and AIDS are even more intimately connected. Both have been episodes in a long series of miscalculations emanating

from a single ongoing, self-propagating scientific program—microbe hunting. Microbiology certainly achieved many notable scientific discoveries, especially early in this century. Polio marked the end of the infectious disease epidemics that once ravaged the industrial world. Microbe research has mostly outlived its usefulness, leaving virus and bacteria hunters with little to accomplish, yet they still dominate the increasingly well-funded science establishment. As a result, they have for three decades been misleading science and the public about medical conditions ranging from cervical cancer to leukemia, from Alzheimer's disease to hepatitis C, and many more. All these smaller programs are failing in their public health goals as they prescribe the wrong treatments and preventive measures, while generating unnecessary fear among the lay public.

SMON did not mark the first time microbe hunters falsely blamed viruses or other microbes for noninfectious diseases. "Pellagra is a classic example," Reisaku Kono emphasized in retrospect. "It was once believed to be a communicable disease and, as is well known, Goldberger swallowed fecal extracts of the patients to destroy this notion."[21]

Pellagra, the quintessential human tragedy representing the era of the bacteria hunters, has been too widely forgotten. Chapter 2 tells the story of Goldberger and other scientists who fought the excesses of the first microbe-hunting establishment.