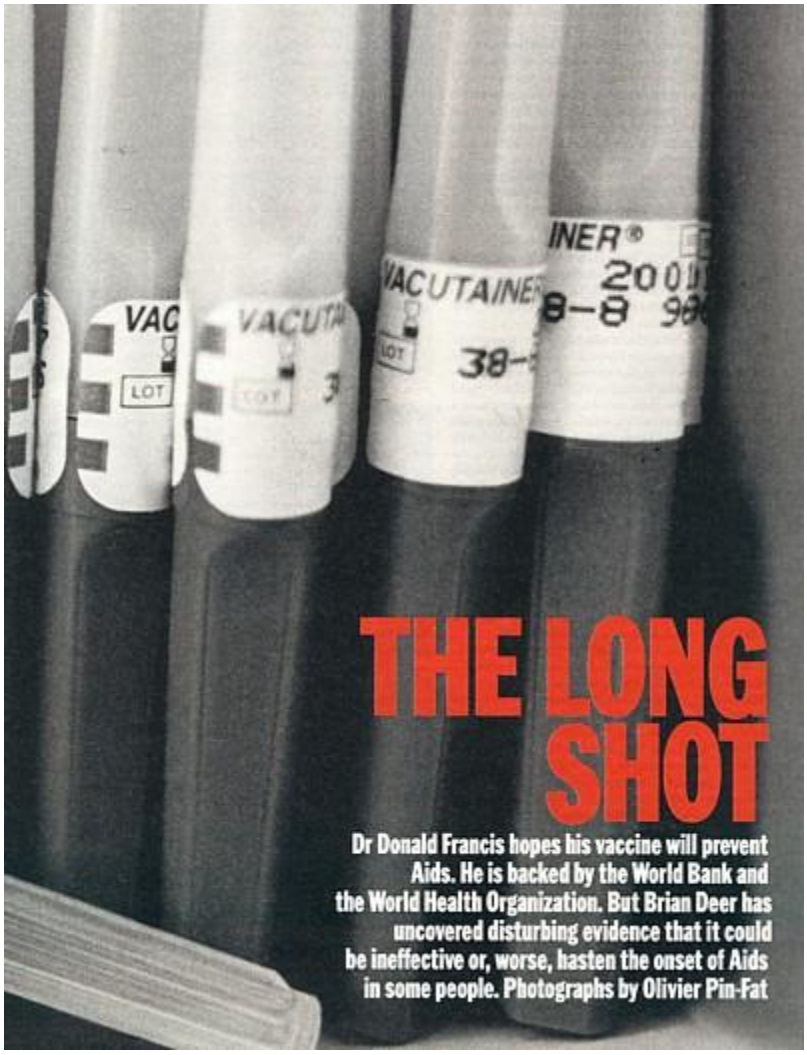

AidsVax: the long shot

Brian Deer investigates "the world's first vaccine against Aids"

The World Bank, the World Health Organization, and HIV groups everywhere rooted for VaxGen Inc of Brisbane, California, and it's "first Aids vaccine", which went into clinical trials in both the United States and Asia during the 1990s. But Brian Deer's Sunday Times investigation proved that it could never work, and even led to a US federal prosecution against one of the key players.

The Sunday Times Magazine, October 3 1999.

AidsVax: the long shot

Dr Donald Francis hopes his vaccine will prevent Aids. He is backed by the World Bank and the World Health Organization. But Brian Deer has uncovered disturbing evidence that it could be ineffective or, worse, hasten the onset of Aids in some people.

The Sunday Times Magazine, October 3 1999

Once a month, at around 3pm, Dr Donald Francis, president of the VaxGen corporation, boards a 747 at San Francisco airport for an 18-hour flight to Bangkok. The route is unpopular - with maddening stops in Seoul, Hong Kong or Taipei - and he insulates himself in a business class window seat with earplugs, eye-mask and face-cream. The tedium drives him crazy, but he doesn't sleep much. His adrenaline levels stay high. Speculations loop like a tape through his head: "What if I do? Supposing I don't?"

He's 57, but looks ten years younger, with blue eyes and an animated style that makes people think that he's gay. When they grasp that he's not (married twice, two sons) the next thing they guess is that he works in show business; say, music or motion pictures. Boyish, fit, articulate, charismatic; he's a person you'd choose to sit next to. But he's a doctor and scientist in the gruesome field of Aids, so demons lurk behind the mask.

I couldn't wait to meet him. We've something in common: we've followed the epidemic since the start. I reported on the first known death in Britain, in December 1981. He was the first to alert America's blood banks, arguing that a virus was to blame. In Randy Shilts's 1987 Aids history, And The Band Played On, Francis storms across 76 pages, warning, demanding, lambasting. In the movie of the book, starring Richard Gere and Anjelica Huston, he's played by Full Metal Jacket's Matthew Modine. He's ER meets JFK.

A man with his record might have taken it easy, sure he'd done enough. In the 1960s, as a young MD with the American government's epidemiology service, the Centers for Disease Control (CDC), based in Atlanta, he was dispatched to India to help eradicate smallpox: a triumph against infectious illness. In the 1970s, while studying virology at Harvard, he was rushed to Sudan by the World Health Organisation - the WHO - to investigate the first outbreak of ebola. In the 1980s, he led trials in Phoenix of a successful vaccine against another killer, hepatitis B.

But for him these achievements merely judder like turbulence; they remind him of what's still to be done. When he slips into Bangkok the following morning, his destination is Taksin Hospital, by the Chao Phraya river, a corroded-concrete and grimy-glass hulk full of poor people patiently waiting. He goes to the second floor and through a pair of glass doors, where the atmosphere transforms. There are maroon carpets, soft furnishings and secretaries in beautiful dresses. A sign inside says: "Bangkok Aids Vaccine Evaluation Group". The VaxGen experiment.

People laughed when he declared - seven years ago - that he would be first with a shot against Aids. After 20 years as a fireman with the CDC, everybody said that he couldn't focus on such an intricate project. Although he'd set-up an Aids lab back in 1983, ten minutes at a bench would have him yawning and twitching. He preferred khaki shorts to white coats.

Since the human immune deficiency virus was discovered in 1984, moreover, it has been the definitive white coat challenge - and quite different from his previous foes. Unlike smallpox - an easy target- HIV kills some of the very cells (so-called T-helper cells) which are fundamental to our immune system defences. Unlike ebola, a rare disease, HIV has slayed 14m people and infected another 35m. And unlike hepatitis B virus, which is quite stable, HIV is a so-called "retrovirus", with its genes coded in ribonucleic acid (RNA), and changes so much with each replication that it breeds an infinity of strains.

When Francis was at medical school in the 1960s, a virus was a virus, with maybe three strains, like polio. Vaccines were easy. But such is HIV's frenetic shape-shifting that each infected person harbours an astonishing swarm of strains, totalling about 1 billion, all slightly-different, virions. Scientists lump them into two types (HIV-1 and HIV-2), three groups and ten subtypes. Thousands

of strains are studied. At med school he learnt that parasites evolve to live in harmony with their hosts. But HIV is so new and unstable in humans that it may evolve to become a quicker killer, or be more infectious. The truth is, nobody knows.

Cleverer doctors and scientists than him have got lost in this terrain. So far, some three dozen would-be vaccines have been tested in labs, animals or a few individuals, but none has done any good. Vaccines work by priming our immune systems - including antibodies and T-cells - so that they will be ready for action if a bug comes along. But so far every attempt to accomplish this with HIV has either proven dangerous or to have no effect. Some experts say that nothing will work.

Francis crosses the Pacific with an approach to the problem that sounds beguilingly simple. The VaxGen experiment is with a product - brand-named AidsVax - that mimics part of the viruses skin, or envelope. By inoculating healthy people with a manufactured clone of this part - a sugary "glycoprotein" called "gp120" - antibodies are supposed to be primed to protect in the event that sex, blood or drug misuse causes the virus to later intrude.

At Taksin Hospital he fine-tunes the experiment - a "placebo-controlled double-blind trial" - so far the only full-scale Aids vaccine trial ever. On 24 March, the first of 1,250 HIV-negative Thai volunteers started on a course of seven six-monthly shots. Another 1,250 are getting an inactive placebo. Who is getting what is concealed in codes, and any difference in the numbers who later become HIV-positive should reveal if the product works.

Francis meets with Dr Kachit Choopanya, his principal investigator. In silk suits and gold-rimmed glasses, Kachit, 65, controls 17 Bangkok drug dependency clinics, chosen to take part by Francis's old friends at the CDC and WHO. Heroin misusers are top of the HIV risk-list, due to poverty-driven needle-sharing. If they can be protected, the agencies reason, then you, I, or anyone can. "If the VaxGen vaccine can create immunity in humans, then we can solve the whole problem," Kachit declared on the day of the first jab. A 27-year-old heroin addict was equally upbeat. He said: "I believe the trial could bring great benefit to mankind."

There's a similar impression at a high level in America that history may be about to be made. The US government's National Institutes of Health and its Food and Drug Administration, both in Maryland, are backing the experiment. So are officials of the World Bank in Washington and United Nations agencies. And so is the principle lobby group: the International Aids Vaccine Initiative. The group's president, Dr Seth Berkley, said: "We applaud VaxGen."

Francis basks in these endorsements. He settles on the thought that he'll do it. VaxGen is one quarter owned by Genentech Inc, a medical biotechnology leader. Genentech is a subsidiary of Hoffman-La Roche, the Swiss pharmaceutical colossus. All are poised for full-scale production. When shares in the company were launched on the New York Nasdaq market at the end of July, they jumped from $13 to $26. He banks on a license for a crash programme of inoculations like the world has never seen.

But when he flies in from San Francisco, he can never quite quell his anxieties. In his files are papers which suggest that AidsVax can't really work. And he's familiar with scientists who warn of possible hazards on a globally catastrophic scale. His vaccine may make it into millions of people. The profits could buy Bangkok. But the momentum behind the experiment could turn out to be one of medicine's greatest mistakes.

At first glance, Thailand is a strange location to carry out medical trials. The CIA rates the country as merely an "emergent democracy"; the last military coup was only eight years ago; and there were Bangkok riots in 1992, when 91 died or went "missing". Corruption is de rigeueur, while police are

accused by Amnesty International of "extra-judicial killings". Much of its profile relies on sex: first with young women and later with children.

Since the coup, however, quick cheap, experiments on the Thai population have been added to the country's attractions. Dozens of projects are currently in progress, run by foreign pharmaceutical companies and sponsored by the CDC and WHO. With an estimated 800,000 Thais infected with HIV, Aids is the big one, with tests of drugs, immune-system stimulants, and top of the list Francis's AidsVax trial.

It makes sense to test products where the risk of Aids is greatest, but my attention was drawn to potential problems during a conference in a Bangkok hotel. The topic was Aids vaccines. Francis spoke. And a doctor pointed out that some volunteers in an AZT trial were mothers from remote hill tribes. "They come across the border from Burma." he said. "They don't speak Thai, so there is the question of whether they can understand enough to give informed consent."

The question was brushed aside ("They keep coming back.") and might not have meant much if I hadn't also met an activist from the northern town of Chiang Mai. Despite grilling 11 people who swallowed tablets daily, he complained that he couldn't discover even the name of the product or the pharmaceutical company involved. This man was a former heroin user, so I asked him where VaxGen was recruiting. "Go to Khlong Toei," he said. "By Port Authority Building. That's where they'll get people for the trial."

Khlong Toei is a slum; a sewage-stinking wasteland; a cauldron of disease and drug use. The better-off live in concrete hutches, with wire-fenced windows and balconies. Next down in the social scale are wooden-shack coops on plots of flood-prone ground. Then there are kennels: festering shantytown alleys of plank, sheet-iron and debris sheds. The "streets" are dim corridors, with boardwalk floors, cluttered with children and dogs. At night frail figures shuffle around, suffering from Aids, tuberculosis or both.

Thailand was once praised for anti-HIV efforts in disease hot zones such as this. But evidence suggests that since the 1992 coup priorities have changed. In 1992, a health minister complained that talk about the virus had "seriously affected tourism". And now, official figures show that Aids prevention has been slashed by one third against comparable public health programmes.

The biggest cuts have been in initiatives aimed specifically at drug misusers. "There used to be a project for clean needles in the early 90s, but now it's gone" a spokeswoman for a Khlong Toei charity, the Duang Prateep Foundation, told me. A health department official said the same thing. His time-frame: "about seven years ago". Targeted education, known to be most effective, has also been axed, he said.

Nobody could explain the thinking, but the effect on the junkies can be measured. Blood tests reveal that HIV prevalence peaked among female prostitutes in 1993 - when 30% were positive - and has since fallen back to 21%. Among rent boys, prevalence peaked in the following year at 18%, and is now half that figure. But prevalence among heroin-injectors has leapt from 31% in 1994 to a staggering 47% now.

Were these changes evidence that the government were allowing the junkies to be put at greater risk to make them useful for experiments? (Health department officials told me that if AidsVax is marketed, they expect a billion-dollar manufacturing plant.) I couldn't find out. People wouldn't talk when I raised such contentious concerns. Even Bangkok's Medicines Sans Frontieres staff went silent when asked about the trial.

Francis is convinced that nothing is amiss, and his collaborators voice no worries. "All have assured me that this has been done ethically," he told me, when eventually we met. "We are going out of our way not to increase the vulnerability of an already vulnerable population." The trial was conducted in Thailand, he said, for scientific reasons. Different parts of the world are linked with different HIV subtypes, with their myriad subsidiary strains. B subtype strains, for instance, are most common in North America, Europe and Australasia; A, C and D in Africa. In Thailand, there's a mix of B and E strains and, for technical reasons to do with E strains, the company argues that success is more likely there "than anywhere else in the world."

But there are aspects of the project which suggest that the junkies may be involved in an unusual way. A parallel trial among gay men at American clinics is having problems finding and keeping volunteers, due to scepticism towards the venture. But at Kachit's clinics the programme has features which may help to avoid these snags. The junkies get methadone, an oral heroin substitute, plus $10 expenses for each of up to 17 visits. The risk is the appearance of offering drugs and money as inducements to this desperate group.

There's also a feature of the experiment's design that seems self-contradictory. If the methadone liquid got people off injecting heroin, the volunteers' risk of infection would slump and they would be of little use to the vaccine trial. In fact, documents drawn up with the CDC and WHO show that that 7% of clinic users are expected to become HIV-infected each year. So, despite the oral methadone, they keep injecting heroin. They may even buy it with VaxGen's money and have an increased risk of getting Aids.

The logic of the trial creates a dilemma for Francis. The moral uncertainties about using junkies as guinea pigs might be offset by humanity's greater needs. But there would need to be plausible scientific grounds to think that AidsVax might work. And on that the VaxGen experiment is open to even greater doubts.

When Francis returns from his trips to Bangkok, it's to Brisbane, a community on the San Francisco peninsula, midway between the city and its airport. His home and workplace both looks eastward across the bay: towards Oakland and, beyond that, America. His home is on a hill and lined with Chinese paintings. His office is by the shore, in black glass.

He huddles weekly with his senior colleagues: VaxGen's vice-president, Dr Phillip Berman, and its chairman, Dr Robert Nowinski. Berman, aged 49, is a molecular biologist. He's heavy set with curly hair and has laboured on the science for 15 years. Nowinski, 52, is bald and wears glasses. He's a biotechnology entrepreneur from Seattle. His main claim to fame is having founded and sold a company, ICOS, which boasts Microsoft's Bill Gates as an owner.

The key document at many of their sessions is a "special issue" of a prestigious journal, called Aids Research and Human Retroviruses. It's dated last October. Twenty papers are inside and they're a rave for VaxGen's ideas. Dr Seth Berkley, the International Aids Vaccine Initiative's president, declares that politics and economics are bigger obstacles to progress than "a scientific barrier". Dr Mary Lou Clements-Mann, a researcher for a rival company's vaccine (and who died in a Swissair plane crash off Nova Scotia last year), shrugs off pessimistic "misperceptions". Dr William Heyward, the CDC's Aids vaccine chief, argues that "only through such trials" as the Bangkok project "will further knowledge be gained".

When visitors drop by, Berman outlines his own paper. It sets out how AidsVax is meant to work. "Many lines of evidence suggest that a strong antibody response to the HIV-1 envelope glycoprotein," he explains, "will be an essential feature of any Aids vaccine." Berman sketches what

this means on a board in the conference room, across the corridor from Francis's office. The billions spent on Aids have produced unparalleled insights on HIV, which are the platform on which he builds. The virus infects. The immune system checks it with, among other things, specially-tailored antibodies. But the virus mutates around these adversaries. So the immune system tailors new defences. The virus then mutates and immunity responds. It's like a leapfrog competition. Eventually, the immune system tires of all this leaping, packs up and then it's Aids.

Of all the different parts of HIV, the envelope glycoprotein gp120 is the part that mutates the most. This sits in blobs around the virus, like loose balls of wool, on the tips of protruding spikes. Berman zooms on the moment a blob meets a cell, which is 1m times bigger than the virus. Part of the blob's surface locks onto a receptor (like a data-port where cells get information). The blob then unravels and locks another of its parts onto a second sort of receptor on the cell. This cues the cell to pull the virus inside. Infection is complete.

Here, Berman argues, is where AidsVax helps: by blocking this double-lock connection. Summoned in advance, due to earlier vaccination, antibodies stick to key parts of the blob and so stop it from locking on the cell. If the virus is a burglar, these antibodies are bullterriers, waiting for a leg to appear through the window on which to snap their jaws. Once they've got hold, the virus is paralysed, to be disposed of by other kinds of cell.

He makes things sound simple. Visitors are impressed. Investors wonder: why dither in Bangkok? But the science expounded in the journal issue doesn't convince many people who grasp the detail. "It's a waste of time," Dr Robert Gallo, America's pre-eminent retrovirologist, told me. Prof Andrew McMichael, Aids vaccine chief at Oxford's Institute of Molecular Medicine, said: "I wouldn't have the belief that this will work." And Dr Jean-Paul Levy, head of France's vaccine programme, spat: "It forgets one century of science."

For all the plausibility of the journal's special issue, the most detailed analysis of VaxGen's approach was published in February last year in the Journal of Virology, an even more influential publication. More than 500 people - mostly American gay men - took part in preliminary tests of gp120 in the mid-1990s but experts at seven of America's leading research centres found that, despite the shots, 16 vaccine recipients became infected with HIV. That's more than 3% of those getting vaccine, roughly the same percentage as those on placebo.

Molecular biologists were not surprised, although their critique is extremely technical. What it boils down to is that if HIV leapfrogs the immune system - with all its astounding complexity - it will easily do the same with antibodies induced by an off-the-shelf manufactured product. Inducing antibodies to one B strain, or two E strains, or five, or fifty XYZ strains, is like buying insurance against being hit by cars with specified license plates.

VaxGen's answer is to develop products from strains it claims provide "cross-protection" against others. In Bangkok, for instance, the vaccine is AidsVax B/E, including gp120 clones from one B and one E strain. The B strain was isolated from a six-year-old New Jersey boy in 1984, while the E strain was collected from a soldier in Chiang Mai about nine years ago. The plan is to mix 'n' match vaccines in this way to suit the subtypes in different parts of the world. Berman zooms closer and claims that parts of gp120 stay sufficiently constant between the mutating strains to offer a point of attack. Like all proteins, the blob is made from amino acid molecules, which string together like beads in a necklace to make the loose balls of wool. Each bead is made from one of a possible 20 amino acids. Letters are used to denote these acids: G stands for glycine, for instance, R for arginine and Q for glutamine.

Berman says that the vaccine needs to copy the amino acid sequence at a key point in this string. Near to where gp120 locks onto the cell, there is a loose loop of "wool" - not 100 millionth a cell's size - which biologists call V3. Berman zooms again: to the tip of this loop, a string of just six necklace beads. Here, he argues, is a segment that remains more constant than most and induces antibodies which will stick and stop the double-lock connection with the cell. All it needs is for the vaccine and the virus to have the same acids at the tip of this loop.

Using this argument, Berman deduces that the early tests of gp120 offer hope for the experiment after all. Mostly, volunteers studied for the Journal of Virology were injected with gp120 cloned from the New Jersey strain, in which the necklace in the V3 loop's tip has the beads GPGRAF (meaning: glycine, proline, glycine, arginine, alanine, and phenylalanine). It's a common configuration in North American strains. But Berman argues that some of the volunteers who became HIV-positive despite being vaccinated were infected with strains in which the loop was different: say, GPGRVL (ending with valine and leucine instead). This, he suggests, was why the gp120 didn't protect them. With the commoner strains he believes it did.

At VaxGen's offices, this bottom-line is dazzling. The "special issue" paper quickens pulses. But additional information reveals an oddity, which Berman's presentation overlooks. At the American government's Los Alamos National Laboratory, in New Mexico, staff track amino acid sequences for thousands of HIV strains. And when I asked them to print their data from Thailand, a startling contradiction emerged. The B component in AidsVax B/E - the shots being given to the junkies - has the New Jersey V3 loop tip sequence. It goes: GPGRAF.

According to Berman's argument, the local B strains would need to have the same string of beads. But only 10% of Thai B strains have the New Jersey amino acid sequence. Far more often - in nearly half the strains - there are two different beads in the loop's tip: glutamine (Q) and tryptophan (W). They are GPGQAW. By Berman's own reasoning, the Bangkok junkies are being injected with the *wrong* vaccine.

Every six months, a ten-strong committee of doctors and scientists crowds into VaxGen's boardroom. This is the "data safety and monitoring board", recruited to keep an eye on the experiment. On one side of the table sits a Harvard infectious disease specialist. On the other is a Yale ethicist. There are three Thai physicians and a Seattle statistician. Dr Walter Dowdle, a former CDC deputy director, presides. The Americans are casual, in open-necked shirts, but Dowdle runs proceedings with care. Piled around the table are printouts on the volunteers, with blood tests and other results. Using codes which nobody else gets to look at, they can see who's getting AidsVax and who the placebo and whether any difference the number of HIV infections has emerged between the groups.

By the convention for vaccines, any difference would be vast for the product to be declared effective. Measles vaccine, for instance, is 95% effective, tetanus 90%, and hepatitis B 85%. But the committee's brief is to watch for just 30% effectiveness. Such is the threat from Aids, it's argued, that this figure is enough for success.

I asked a professor of medical statistics to number-crunch this percentage. To reach the 30% mark, he said, there would only need to be 28 more infections among junkies on the placebo than among those receiving AidsVax. If VaxGen recruits 2,500 - and on its assumption that in a year about 7% (87 people) on placebo will become infected due to needle-sharing - then if the number who become infected after getting AidsVax is 59 (4.7%) or fewer, the committee can rule that the product works.

VaxGen critics think that even this meagre difference couldn't appear, and that Dowdle, 68, will one day emerge to drape a consoling arm on Francis's shoulder. But an alternative scenario is predicted by some with long research experience. Nobody can recall an HIV product being ditched after reaching a full-scale efficacy trial. And, such is the desire for "something to be done" about Aids that science could be pushed to one side.

The most powerful pressure for something to be done comes from the White House, anxious to appease the Aids lobby. In May 1997, President Clinton threw his weight behind urgent action. "If the 21st century is to be the century of biology," he declared. "Let us make an Aids vaccine its first great triumph."

How such pressures can translate date back to 1989 and the first anti-Aids drug, AZT. A board like Dowdle's monitoring a trial among HIV-positive volunteers with no obvious illness, saw data suggesting that full-blown Aids could be prevented. At the time, AZT was licensed only for terminal disease, but this finding caused the trial to be halted and the product to be approved for this use. But the decision was based on a transitory data "blip", which had caused the board to act prematurely. A longer study, published four years later, found no preventative effect.

Stopping trials in this way before their scheduled completion is now standard in Aids product development. "If efficacy is observed at the time of a scheduled interim efficacy analysis," Nowinski explains, "the monitoring board will recommend termination of the trial."

But could bodies such as the Food and Drug Administration and the European Medicines Evaluation Agency license a vaccine that doesn't work on the basis of an AZT-style blip? Evidence suggests that agencies under political pressure take just such paradoxical steps. The National Institutes of Health, for instance, vetoed the VaxGen experiment as a waste of money and volunteers. But after being accused of "a human rights violation" by Dr Jonathan Mann, 51, former WHO Aids chief (and who died with his wife, Clements-Mann, also 51, in the Swissair crash), the institutes not only reversed themselves, but granted Francis $4.6m.

Sometimes the clamour may be marshalled by persons who may not be as detached as they seem. The Journal of Aids Research and Human Retroviruses, for instance, has an editorial board that's a Who's Who of Aids. But Francis paid the publisher $10,000 for the "special issue", which Berman edited as a "guest". As for some of the contributors, Francis helped to set up Berkley's international vaccine initiative and advised Bill Gates's charity foundation to give it $25m. He has done a deal to supply proteins to the rival manufacturer which employed Clements-Mann. And he has offered the CDC's Heyward the post of VaxGen vice-president, starting next January.

Pressure also comes from powerful bodies which have long-held institutional agendas. The CDC, which mostly collates disease data, first became a significant health service body due to polio vaccine, launched in April 1955. The WHO's singular success was smallpox eradication, accomplished in October 1977. Mass immunisation is what they know best. It's simply what they do. "Don Francis reminds them of when they were young," Dr John Moore, of New York's Aaron Diamond Aids Research Center, told me.

What worries critics such as Moore is that political and institutional pressures may lead to millions of people being injected with AidsVax before the benefits and risks are clear. The WHO estimates that annual demand for the first vaccine will be 650m doses and UNICEF leaders are thinking about adding it to programmes for 100m children.

Francis anticipates that the CDC, which has already granted him $8m, is to finance a US immunisation campaign and, in Europe, national health services will pick up the tab. "In addition,

the International Aids Vaccine Initiative has started a campaign to fund the development and purchase of an HIV vaccine for the developing world," VaxGen documents say. "In meetings with us, the World Bank has indicated that it's exploring the potential for low-interest loans to support the purchase."

One of the snags which may be overlooked in this rush is the effect on recipients' behaviour. Common sense says that somebody who thinks that they may be protected is more likely to take chances with risky activities than a person who knows that they aren't. One study of this effect in 1997 found that unsafe sexual behaviours doubled among gay men in preliminary vaccine tests. If this was repeated globally, the impact of an even vaguely effective AidsVax may be that the Aids epidemic gets worse.

South of VaxGen's offices, the next freeway exit gives access to its powerhouse: Genentech. This is the world's front-runner in medical biotechnology, with seven licensed products, from human growth hormones to a clot-buster, Activase. Twenty years ago the company was all dreams and venture capital; its few staff snipping and splicing genes in a wasteland where shipyards had died. Today, their ranks of Mercs and BMWs surround 26 buildings in biology's Silicon Valley.

Stopping by from time to time are visitors from its master, the druggernaut Hoffman-La Roche. With twin headquarters in Basle and New Jersey, and sales last year of SWf24.7bn (œ10.2bn), this vitamins-to-Valium giant has the marketing muscle should AidsVax come on stream. At its own labs, Roche shuns the vaccine race, but with taxes pledged to line-and-jab Africa and Asia executives doodle in billions on the hope that Francis pulls it off.

When I flew to San Francisco to quiz Francis for this story, Berman was ecstatic, in jeans and a check shirt, over a new $1.4m vaccine facility. The experiment produces a torrent of clinic samples; each volunteer gives blood on 17 visits, and each sample is split for tests. Giant freezers were being installed to store bar-coded specimens. There could be 400,000 in all. There's also a $500,000 microbiology kit going in: DNA sequencers, PCR machines, centrifuges and the like. Soon he would direct 30 staff in 20 rooms. He was like a seven-year-old on Christmas Day.

The first thing that struck me was the push of the spending, irrespective of scientific achievements. Apart from all the investment so far, Genentech had a 10,000-litre fermenting tank, half full of New Jersey strain vaccine. Nobody wanted that, worth $1m, flushed away, much less the careers of its makers. The next thing I noted was the standard of safety imposed on the facility's construction. To handle a dangerous pathogen in California, the brown-and-yellow building, made from tipped-upright concrete slabs, was stamped with certificates and permits by the box load before the first plank was sawn. It's both earthquake- and microbe-proof. And its forests of copper pipes, air ducts and bio-filters were tested to tolerances few structures could endure.

But while regulations make sure that the building is safe, critics say that the product itself escapes much rigorous scrutiny. With vaccines, any problems often don't appear until mass-market use, and such is the head of steam building up behind Francis that sceptics think that if AidsVax doesn't join the annals of useless shots, it has the potential to join, say, a 1960s measles vaccine that made the disease in those infected worse.

What worries some scientists is that because AidsVax provokes antibodies to its own specific gp120 strains, there's a risk that it may actually suppress the immune system's ability to combat other strains. On this thinking (the principle is sometimes called "deceptive imprinting") even if the junkies were protected against the New Jersey and Chiang Mai strains, they might die more quickly if they

get infected with one of the countless other mutations. "There's nothing new in this," Dr Heinz Kohler, who has led investigations at Kentucky University, said. "It's just common sense."

At Kansas University, researchers have found that monkeys injected with gp120 and then a hybrid kind of HIV had more of the virus in their blood later on than infected animals which weren't vaccinated. "The question is: will those people who are vaccinated progress to Aids more quickly if they become infected with HIV than those who were not vaccinated at all?" Prof McMichael at Oxford summarised. "We might not know the answer for 10 years."

No such problems were revealed in the preliminary tests, but despite the importance of long-term follow-up (recipients of the hepatitis B vaccine that Francis worked on in the early 1980s have been tracked for two decades), VaxGen no longer monitors what has happened to the people who received its product in the mid-1990s preliminary tests. Francis argues that it makes more sense to wait for the full-scale trial results.

This apparent loss of data is surprising to some, because history warns of the pitfalls of not being thorough. In 1955, just one month after a near-hysterical press conference in Michigan launched polio vaccine, reports poured in to the CDC of hundreds of children going down with the disease, induced by the shots themselves. President Dwight Eisenhower said that, because of the "great pressure to bring this out", scientists may have "short-cut a little bit".

AidsVax cannot give volunteers Aids, but there may be something even more terrifying than the anxiety that it might accelerate their disease if they are later infected with HIV. Some scientists think that, if it works at all, the product may have a dangerous effect on the evolution of HIV. Five years ago, Los Alamos scientists declared that there was "no simple answer" as to whether Aids could become contagious through coughs and sneezes - and other researchers argue that, in much the same way as a partial course of antibiotics can promote resistant bacteria, so a poorly-effective vaccine may promote more deadly and infectious strains.

This may sound like journalistic scare, but HIV's best-understood RNA cousin is influenza virus, which produces devastating mutations every 20 or 30 years. Hepatitis B virus, meanwhile, has already produced mutant strains accepted as being vaccine-induced. "When you use a vaccine, you are introducing another selective pressure," Dr Paul Ewald, professor of biology at Amherst College, Massachusetts, explained. "It could make the problem more damaging, or less damaging, depending on the antigen you use."

Researchers told me that, compared with the potential risks to volunteers, this doomsday scenario was "unlikely". But with agencies standing by to jab hundreds of millions of people, some wondered if, for our species' safety, "unlikely" was reassuring enough. "My personal view," Dr Art Ammann, president of the San Francisco-based Global Strategy for HIV Prevention, and a former AidsVax researcher, said, "is that we could face a global nightmare."

And the Band Played On was a monster hit in America, and Shilts, the author, makes two observations about Francis from before the vaccine race. Noting his early career in medicine, virology and diseases such as ebola, Shilts notes that when Aids first appeared "Don Francis viewed his life as an accumulation of chance decisions that had put him in the right place" to respond. "Francis had a penchant for quick conclusions stated in the most dramatic terms," he adds, with "a reputation for singular brilliance." Like teachers' praise or schoolyard snubs, people soak up their own publicity. And as I skimmed the book's index in a Motel 6 before the first of two interviews with Francis, I couldn't help thinking that, whether this penchant and reputation were real before the book, they would have been after the movie.

I was startled, even so, by the confidence of his performance, in his office overlooking the bay. There was a Japanese poster for the movie on one wall. On another was a mounted Philadelphia Inquirer report in which he featured as an angry young man. He'd a red-framed sign above his desk for reporters to note. It said: "Joyful participation in the sorrows of the world."

In our first encounter, he fed me his experiment in digestible, barbecue chunks. Wearing jeans, baggy shirt and loose-fitting waistcoat, he paced and waved his arms. There were "perfectly good arguments on either side," he said, "for this vaccine working or not working." Then he leant on a chair, stared moodily across the water and whispered: "I hate this bug." That was a line from Outbreak, a Dustin Hoffman movie, and he'd other such memorable nuggets. "I spend much of my time protecting myself from my concern," he told me.

I thought, Dr Francis, *please*.

It wasn't that I doubted his compassion. Both of his parents were doctors, in northern California; the young Donald grew up to watch flower power bloom and die. At med school in Chicago, he volunteered at free clinics. He was secretary of Physicians for Social Responsibility. He was *for* civil rights and *against* the Vietnam war. His resume was impeccable. But he admitted to never having gone to Khlong Toei, or other slums where his subjects were recruited. It was an awkward omission for the ebola-buster, now on $300,000 a year.

Success with AidsVax would make his fortune, but I didn't think that money drove him on. Chewing over old times, as veterans do, we talked about the moment in 1984 when French scientists discovered the virus. He'd set up a lab at the CDC, but told me that he'd looked for the wrong type of bug. The Americans thought it would be a leukaemia-type infection, but the French hunted for a simple cell-killer. Were it not for this bungle, he seemed to imply, he might have risen at some heady press conference to be acclaimed as the discoverer of the cause of Aids.

He didn't crave something that we all don't dream of. What he was doing seemed oddly human. He'd blown it once, I took as the lesson. He didn't plan to blow it again.

Our next interview was two days later. It was a formal tape-recorder job. After an hour in the company's data room, where modems blink and chatter, I asked him to explain the anomaly with the vaccine. The amino acid stuff. If Berman's theory about V3 loop tips was right, then surely the gp120 from the New Jersey strain wouldn't do much good in Bangkok. Francis had an answer. True, the V3 tip on the B part of the vaccine wasn't the same as the Bs in circulation. But, he said, it *was* the same as on the other prevalent strains - the Es. It would work on them. "It happens to be identical to the Thai E that's in that vaccine," he said.

But this wasn't right. What he said wasn't true. "No it's not," I interrupted.

"Yeah," he insisted.

"No it's not."

"It is."

I rummaged through my papers and read him the amino acid strings from the V3 tip on the gp120 blob. It was not one hundred millionth the size of the infected cell, but not totally out of sight. "Here we are: Thai E strain is GPGQVF."

"Right," he agreed.

"The Thai B strain is GPGQAW," I continued. "If you take the B vaccine sequence it's GPGRAF." The strings were all different. He was talking nonsense.

"Okay, okay," he acknowledged. "I'm sorry."

That surprised me. Lives were at stake. "But you're not giving the Bangkok junkies the most promising product, by your own reasoning."
"For the B virus?" he said. "Possibly. That possibly could be true."
"Isn't that unethical?"
"No." He paused. "No, because it would be unethical if you told them that this vaccine was going to work. We tell them to assume no efficacy."
Ah, yes.
Later I put to him the safety issue and the fact that serious opinion suggested that AidsVax could have long-term risks.
"I think you have to have a theoretical rationale why it would cause harm," he replied.
"There *are* theoretical rationales."
"Where?" he snapped. He was beginning to sound annoyed.
I cited the "deceptive imprinting" work of Kohler in Kentucky as one example.
"The question that you're asking is: if you get infected, subsequently to immunisation, will you have an increased disease manifestation, or harm accrue from the vaccine? And that could be. That could be."
Okay. Nobody was telling the Bangkok junkies. "Don't you think some of these doubts should be made plain in the informed consent?" I asked.
"I think it's more important to say 'we don't know'," he responded irritably. "And that's what we say. And we say: 'do not depend on this vaccine, we do not know if it has effect, if any, and that's why we are studying it'. I think that's your ethical responsibility - to really say: 'We do not know. We do not know if it will cause harm. These are the data that we have.'"
HIV was uniquely dangerous, he said, with 16,000 new infections daily. There was no way to develop the desperately-needed vaccine that didn't involve taking risks.
I said: "But the fact that this is an extremely virulent and infectious agent doesn't entitle you to be reckless."
"Agreed," he hit back. His voice was rising. "But shouldn't it stimulate society to take chances to prevent it?" He said that vaccine developers had always taken risks, sometimes proportionately even greater for less threatening parasites, such as in, say, measles or pertussis. "We have taken the potential risk to deal with diseases that have very low mortality rates," he shouted, stabbing his finger. "With HIV, at least you have the luxury that this bug is so fucking dangerous that it kills everybody - that all *you* can say is that I would do to these people is shorten their incubation period - which would be a tragedy." He glowered at me. Now he'd lost it. It was character revealed by stress. *"But I'm not going to kill any more people than the virus has already killed*."
When his rage subsided, I drove him home and we sipped a couple of beers. The view from his house should had been magnificent, but a fog had settled on the bay.