Pneumocystis pneumonia can be prevented. Why did it take so long for well known preventative measures to be introduced in AIDS?

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"As many of you know, in 1977--four years before the first case of AIDS--a placebo-double blind study by Dr. Walter Hughes and colleagues proved that two double-strength bactrim tablets a day can essentially prevent PCP. Without spending a cent, the federal government could have saved countless lives if only it had urged physicians to consider PCP prophylaxis. At the very least, prophylaxis should have been the standard of patient care for someone with AIDS who had survived one bout of PCP.

I asked a CDC statistician how many AIDS-related PCP deaths had occurred since the beginning of the epidemic. How many Americans have needlessly suffered and died from PCP because of the lack of federal leadership on the issue of PCP prophylaxis?

According to the CDC, as of February 20th, 1989, 30,534 Americans had died of AIDS-associated PCP.

I repeat: 30,534 United States citizens have died from a disease which at least since 1977 has been essentially preventable"[i]**.** ***Michael Callen, AIDS patient and advocate.***

Pneumocystis carinii pneumonia (PCP) was the most common fatal opportunistic infection during the early years of the AIDS epidemic in the US. Although the causative organism may have been renamed Pneumocystis jiroveci , I will still call it PCP as this is the designation by which it continues to be commonly recognized. The taxonomy of this organism has also been reconsidered; it is now generally classified as a fungus.

In the US, the AIDS epidemic was first recognized in gay men; they were thus the group first to succumb to this pneumonia. However, PCP was previously well known as one of several infections that occur in individuals in whom cell mediated immunity is impaired.

There are two broad subdivisions of the immune response, those mediated by antibodies – humoral immunity, and those responses mediated by cells of the immune system – cell mediated immunity. Cell mediated immune responses protect us from certain infections, generally those caused by micro-organisms that require living cells for their growth. These infections, including PCP, are predominantly seen in AIDS.

The known causes of disorders of these two general types of immune response are quite numerous. They include some congenital disorders, some cancers, protein calorie malnutrition, as well as intentional immunosuppression in individuals receiving organ transplants.

Because other conditions associated with disorders of cell mediated immune responses had been recognized well before AIDS, the appearance of a particular constellation of

infections and malignancies in association with a previously unrecognized disease indicated that its major characteristic was a disorder of this aspect of the immune response. Thus a new condition had to be added to the catalogue of diseases affecting cell mediated immune responses.

PCP, as noted above, was already well recognized long before the advent of AIDS. We knew how to diagnose and treat this infection. By 1981, we also knew how to prevent it.

Preventing a first episode of PCP is called primary prophylaxis; secondary prophylaxis is the prevention of a recurrence.

In the earliest years of the epidemic we were unable to define which particular patients were at greatest risk for developing a first episode of PCP, and therefore in need of primary prophylaxis. But by 1983 – 1984, it had become evident that individuals who had experienced one episode of PCP carried a 60-70% risk of developing a second and not infrequently fatal episode within a year. At this time we were therefore able to clearly identify a group of individuals who would benefit from secondary PCP prophylaxis.

Despite this early recognition, it was only in 1989 that the US Centers for Disease Control (CDC) issued recommendations for PCP prophylaxis.[ii]

Before this, some individual physicians did in fact offer PCP prophylaxis to their patients who had already experienced a first episode. However, the Federal medical leadership of that time had generally been silent on this issue, and when challenged, discouraged its practice.

As noted in an article published in 2001:

"Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) and thus ultimate head of the ACTG (AIDS Clinical Trials Group), went as far as telling activists attending a 1987 meeting that there was no data to suggest PCP prophylaxis was beneficial and that it may, in fact, be dangerous."[iii] Some years prior to 1987, Michael Callen, an AIDS patient advocate, received a similar response from Dr Fauci, discouraging attempts to prevent PCP in people with AIDS on the grounds that there had been no controlled studies on the efficacy and safety of this intervention in this particular group of patients. Yet this same leadership did not feel there was any urgency to remove this obstacle by promptly conducting the appropriate trials.

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Did the fact that there had not been a separate trial, constitute a reasonable objection to recommending PCP prophylaxis for AIDS patients who had already survived one episode of this pneumonia? While a prophylactic intervention with trimethoprim-sulfamethoxazole (bactrim) against PCP was first demonstrated to be effective by Walter Hughes in children with leukaemia in 1977[iv], its use had been extended to other groups known to be at risk, without in every case conducting additional trials.

There has been no uniformity on the issue of the need for separate trials of PCP prophylaxis for separate groups at risk. In some conditions associated with a risk of developing PCP, prophylaxis is recommended without reserve. At the other extreme, are several trials of PCP prophylaxis in organ transplant recipients well into the 1990s, long after its benefits had been routinely provided to recipients of kidney transplants at several transplantation centers. . The predictable consequence of these trials was that there were significant numbers of cases of PCP in the control group, while almost none occurred in those fortunate to have been randomized to receive prophylaxis, almost always with bactrim. There clearly is a lack of uniformity in practice, and a lack of clarity in theory, on the circumstances that require randomized controlled trials as a condition for recommending a particular intervention.

There has never been any reason to doubt that bactrim prophylaxis would not be as effective in AIDS patients as in other groups of individuals at risk for PCP. However there were reasons to be concerned that more severe adverse reactions to bactrim might occur in people with AIDS. When a higher dose of bactrim had been used to treat PCP in patients with AIDS, adverse reactions to this medication were seen more frequently than in other groups with PCP.

In patients with AIDS who have experienced one episode of PCP, the chance of developing pneumonia again is so high that any reasonable risk benefit assessment would favour the use of bactrim as a prophylactic measure, particularly since its efficacy had been demonstrated, albeit in different groups of patients. Concern that AIDS patients might more frequently experience severe adverse reactions to this treatment was of course justified, but was not an insuperable obstacle. An effective prophylactic dose was found that was generally well tolerated, but it was not until the mid 1990s that bactrim at this dosage became the most common means of preventing PCP, and now represents the standard of care. These adverse effects of bactrim are mostly hypersensitivity reactions, and included fever, rash, bone marrow suppression and abnormal liver function. However, when the prophylactic use of bactrim eventually started, this obstacle was rather rapidly overcome; with the prophylactic dosage used today, one double strength tablet, three times a week, almost all patients with AIDs can receive bactrim without difficulty. And for those who still experience hypersensitivity reactions, these can frequently be eliminated by desensitizing them to the medication.

It bears repetition to state that the use of bactrim as effective prophylaxis was known before the beginning of the AIDS epidemic but it took about 15 years, and probably tens of thousands of deaths from PCP, for it to be used routinely to prevent this pneumonia in AIDS.

Walter Hughes in a 1981 publication had not recommend that separate trials of bactrim for PCP prophylaxis be conducted for groups at risk for PCP other than chidren with leukemia, among whom he had conducted prophylaxis studies. At that time AIDS had not yet been recognized as one of these groups. He wrote the following in a 1981 publication:

"In *considering the categories of patients to be placed on prophylactic trimethoprim-sulfamethoxazole one must estimate the risk of the infection and weigh this against the adverse effects, cost, and inconvenience of the drug. One must also take into account such related factors as the beneficial effects of trimethoprim-sulfamethoxazole in the prevention of bacterial infections (Hughes et al., 1977) as well as the potential hazard from opportunistic fungal infections. When possible one should review the experience in his medical center and determine the attack rates of P. carinii in various types of compromised hosts, and with these data select the categories of patients deemed at high risk for the infection and place these on trimethoprim-su]iamethoxazole prophylaxis. In our experience this has included all patients who have recovered from one episode of P. carinii pneumonitis where the occurrence, or reinfection, rate is about 15%."*[v]

In AIDS the rate of PCP recurrence was about four times higher than the 15% threshold suggested by Walter Hughes as an indication for prophylaxis However AIDS was not yet known at this time and as noted AIDS patients are unusual in showing a higher frequency of adverse reactions to bactrim than other groups of patients.

However as the CDC seemed to finally realize, the risk of a recurrence of PCP was so great that some response was required, and in 1989 the use of bactrim was recommended, at the dosage used by Walter Hughes. This was one double strength tablet twice a day, a dose later revised to one double strength tablet daily in 1992.
It is worth quoting the following passage from the CDC recommendations:

"In 1989, the United States Public Health Service convened a Task Force of experts to consider the expanding knowledge base about prevention of Pneumocystis carinii pneumonia (PCP) among adults and adolescents (greater than or equal to 13 years of age) with human immunodeficiency virus (HIV) infection. This Task Force concluded that the morbidity, mortality, and cost due to PCP could be substantially reduced by appropriate use of antipneumocystis prophylaxis in subgroups of HIV-infected patients known to be at high risk, and developed recommendations for the administration of prophylactic regimens. "

In 1997 a trial of bactrim prophylaxis had finally been conducted in patients with Kaposi's sarcoma, using two double strength tablets a day, the dose used by Walter Hughes. At this dose adverse reactions were seen, but only 5(17%) of patients had to discontinue the treatment.
The CDC recommendations did note that the trial was conducted in patients with Kaposi,s sarcoma, and in a typically pedantic and ultimately absurd fashion, warned us that there was no evidence that prophylaxis would be effective in AIDS patients without

Kaposi's sarcoma. They thankfully stopped short of demanding a trial in AIDS patients without Kaposi's sarcoma.

Evidence supporting the use of a much lower and safer prophylactic dose of 1 double strength tablet three times a week only started to accumulate after the 1989 CDC recommendations[vi].

The recommendations, published by the CDC in 1989 were to use either aerosolized pentamidine or bactrim.. In this way the routine use of bactrim was even further delayed by an unnecessary distraction with aerosolized pentamidine. This costly distraction, lasted about 4 years, and aerosol pentamidine use was largely abandoned. The trials of aerosolized pentamidine will be discussed in a later section.

In 1992, the CDC revised the recommendations: a dose of bactrim of one double strength tablet daily was then recommended. These revisions, while still including aerosolized pentamidine in the recommendations, did note its marked inferiority to bactrim.

Today, low dose intermittent bactrim is the most frequent method of PCP prophylaxis in AIDS, both for primary and secondary prophylaxis.

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Studies with bactrim for secondary prophylaxis could have started around 1984-1985, to determine the optimal tolerated prophylactic dose, as well as the management of hypersensitivity reactions. At the very least, the use of the dosage recommended by Walter Hughes in the 1970s might have been proposed as soon as the great risk of a recurrence was recognized, for those who could tolerate it (as was in fact done in 1989). It was only in the mid 1990s that the current well tolerated prophylactic dosage of 1 double strength tablet three times a week was finally established As noted .there had been absolutely no reason to doubt that bactrim prophylaxis would be less effective in AIDS than in other immunocompromised conditions. We might have been about 10 years ahead in obtaining information on a tolerated and effective dose of bactrim for prophylaxis. Again, there was certainly no reason, since 1984 to withhold bactrim, let alone discourage its use even at the dose found effective by Walter Hughes in the 1970s, for secondary prophylaxis, in patients who were able to tolerate 1 tablet twice a day. . It is difficult to calculate how many of the 30,500 deaths from AIDS related PCP before 1989 might have been due to a recurrence and therefore preventable, but as noted, it is quite probably in the tens of thousands.

A question therefore immediately presents itself. Why, in the case of AIDS, was bactrim, a known preventative measure against PCP, introduced so many years after a need for it had been recognized? To this must be added the question of why this neglect, the consequences of which can be measured in the tens of thousands of lives lost, has received almost no attention

Despite Dr Fauci's objection to Michael Callen, it must be accepted that influences other than the absence of a trial were responsible for the belated introduction of PCP prophylaxis, as the required trials were only conducted in 1987[vii], at least four years after the need for this intervention was recognized. There was a single trial of bactrim in patients with Kaposi's sarcoma, and two trials of inhaled pentamidine in a broader range of patients. Even then, as noted, there seemed to be no sense of urgency as it took yet another two years (and I suppose one could estimate the number of deaths) for recommendations regarding PCP prophylaxis to appear.

Yet another curious and indefensible objection to PCP prophylaxis was raised by Dr Samuel Broder, who was head of the National Cancer Institute. In a 1987 interview, he was able to discourage the use of PCP prophylaxis on the grounds that the introduction of zidovudine (AZT) would make this practice redundant! This objection was raised in the absence of any convincing evidence that AZT could prevent PCP in a significant and durable fashion, if it could do so at all.

Finally, in 1989 the CDC issued guidelines for PCP prophylaxis. At this time it had also become possible to define a group of patients who were susceptible to a first episode of PCP, and therefore would benefit from primary prophylaxis. In June 1989, the Food and Drug Administration (FDA) approved inhaled pentamidine as a PCP prophylactic measure, but FDA approval of bactrim for this purpose had to wait until 1994. Since bactrim had been approved for other uses, it was available well before this, and was included in the 1989 CDC recommendations. It is appropriate to recall that since the beginning of the AIDS epidemic, groups of patients at risk for PCP, other than people with AIDS, were routinely able to receive bactrim to protect them from this type of pneumonia.

The neglect of bactrim, an agent with proven prophylactic activity also resulted in a long and expensive detour on the road to recommendations for PCP prophylaxis. This distraction, lasting about 4-5 years involved the study of inhaled pentamidine as an agent to prevent PCP. Pentamidine is a drug that had been used to treat PCP, but was administered by intravenous infusion for this purpose, and was associated with significant toxicity. As a prophylactic, and even therapeutic agent, it was hoped that this toxicity could be obviated by delivering the drug to the lungs by inhalation as an aerosol. Delivery of pentamidine in an aerosolized form was studied, in San Francisco and at Memorial Sloan Kettering hospital in New York City. . This involved an examination of the performance of different nebulisers, as to be effective, droplets of a desired size had to be produced. It had been shown that the drug was not absorbed if inhaled, and that it could be administered in this way only once a month. In 1987, trials of aerosolized pentamidine for PCP prophylaxis in AIDS were conducted by two community based clinical research organizations. The Community Consortium in San Francisco provided

efficacy data used by the FDA in approving this treatment. . I was the principal investigator of a trial conducted by the Community Research Initiative in New York that provided the toxicity data used by the FDA in the approval process.

Aerosolized pentamidine proved to be inferior to bactrim as a prophylactic agent and was associated with unusual complications. It not only presented environmental hazards, as inhalation therapy could disseminate other micro- organisms, such as TB, but it was ineffective in preventing PCP in organs other than the lungs. Until its introduction the most common manifestation of Pneumocystis infection had been pneumonia. This had been treated with intravenously administered pentamidine or bactrim, (which in some cases could also be administered by mouth). In both instances the drugs were distributed throughout the body. On the other hand, inhaled pentamidine remained in the lungs. Its use in this way for prophylaxis only protected the lungs, and perhaps not surprisingly, a series of new extra-pulmonary manifestations of Pneumocystis infection were seen, such as involvement of the thyroid gland, liver, bone marrow and heart. In addition when this therapy failed to prevent pneumonia, it manifested in unusual ways, leading to diagnostic delays. As noted it was also clearly inferior to bactrim in preventing PCP, and it has long been largely abandoned. It is also of some interest that bactrim is inexpensive, while inhaled pentamidine presented a significant financial burden to those needing it. Because of this expense, patient groups imported this drug from outside the US, where .it could be obtained at less expense.

In all likelihood aerosolized pentamidine was pursued as a possible PCP prophylactic agent because interest in bactrim, was so discouraged by the Federal medical leadership. In this way, dependence on an indifferent authority for guidance led to an expensive and completely unnecessary distraction. As noted, the use of inhaled pentamidine was gradually abandoned in favour of bactrim after the CDC recommendations were issued in 1989.

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The study and use of inhaled pentamidine to prevent PCP remains a curious episode in the medical response to this disease. It serves as some indication of the considerable influence of the Federal research leadership, which chose to ignore an available, inexpensive and tested prophylactic therapy until 1989, on the grounds of its toxicity when used as therapy in AIDS patients. Inexplicably, there were no urgent attempts to address this issue in the setting of the lower dose used in prophylaxis. . This resulted in indifference to, and sometimes a surprising ignorance of the proven prophylactic efficacy of bactrim on the part of patients and their advocates, who had everything to gain, and of

the physicians taking care of them. Act Up, an important AIDS advocacy group issued a booklet called "FDA action Handbook" in 1988, which contains the following inaccurate statement about pentamidine, "*The story of pentamidine, the only drug known to be effective both in preventing and in treating Pneumocystis Carinii Pneumonia (PCP), the leading cause of death in people with AIDS in the USA is a textbook case of the uncoordinated Federal response to AIDS"* Pentamidine of course was not the only drug known to be effective in preventing PCP. Thus while justifiably criticizing one federal agency – the FDA, for its slow approval process, this statement, in a sense pays homage to another Federal agency, the National Institutes of Health (NIH) in following its lead in ignoring bactrim. One must also assume unfamiliarity with, or a neglect of the pre AIDS literature on bactrim and PCP prophylaxis by patient advocates, and in turn of the experts they had chosen to advise them on scientific and medical issues.

It is also curious that in 2001, on the occasion of the 20th anniversary of the beginning of the AIDS epidemic in the US, the introduction of PCP prophylaxis was hailed as one of the two greatest medical accomplishments in the fight against this disease. The other was the development of highly active antiretroviral therapy. Benefits of these two therapies were calculated in terms of the additional years of life made possible by these interventions. These calculations begin in 1989. The triumph of PCP prophylaxis was sadly unable to include those who had died of a recurrence of AIDS related PCP before that year. The numbers are not known, but given the very high probability of a recurrence in those experiencing a first episode, and that this recurrence would occur at a later stage in the disease, it is likely that a considerable proportion of the 30,500 AIDS related PCP deaths before 1989, would fall in this category. It is possible that the poor overall prognosis of AIDS in the early years may also have contributed to the neglect of PCP prophylaxis. Prophylaxis might have prevented death from PCP, but would have been a life extending, rather than a life saving intervention.

It could even be argued, that since the immunologic and hemtologic parameters remained unchanged after a first episode of AIDS related PCP, that the use of secondary prophylaxis would have been a wise clinical decision even before the high rate of recurrence had been recognized. An argument could also have been made for attempting primary prophylaxis in the early years among those with the same immunologic and hematologic parameters as those patients who developed PCP. There had never been any indication that these parameters ever improved.

The use of bactrim for PCP prophylaxis in AIDS can be regarded today as the standard of care. The reasons for the delay in its introduction are much more difficult to address than its recognition. A concern about bactrim intolerance cannot justify the years of inaction regarding its prophylactic use; it was eventually recommended at the dose used in the 1970s. Concern about toxicity is appropriate, but what can explain the long delay in undertaking studies to find an effective and tolerated dosage? This neglect, as already mentioned, has received almost no attention. Perhaps, a problem that requires a complex explanation, if indeed a satisfactory explanation can ever be achieved, may be more

easily neglected. But should it prove impossible to find a clear answer to the question of why it took so long to prevent PCP, despite knowing how to do so, it is at least possible to consider the influences that might have contributed to this result.

There probably was no single agency that was responsible. Rather, the interaction of several factors probably contributed to the neglect of PCP prophylaxis in the first 8 years of the epidemic. These diverse factors include the conventions of medical practice; its essentially conservative nature with a reliance on a respected authority to produce treatment recommendations particularly when concerning a newly recognized disease. The way this authority developed as well as its assessment of priorities obviously played a role as did social attitudes, particularly towards people with transmissible diseases, as well as towards homosexuality and drug use. The AIDS epidemic was also associated with the development of community activism on behalf of affected individuals, at least of a magnitude never before seen. As this activism came to include advocacy regarding specific treatment and research issues, might it have accelerated the process leading to the recommendations, or have been without effect?

An attempt to sort through these complexities might usefully start with a consideration of the circumstances under which the first patients were seen, and then turn to the diverse factors noted above.

In the US, the epidemic was first recognized among gay men in New York City, Los Angeles and San Francisco. In these cities the disease first appeared among gay men who were already patients of a particular group of physicians. Since the mid 1970s, this subset of gay men had been treated for several sexually transmitted infections, and thus had already established a relationship with a physician. In all three cities, physicians had established practices to meet the needs of these patients, which included the freedom to discuss sexual practices and sexually transmitted infections without reserve. The physicians were frequently, but not necessarily themselves gay men; several women were also prominent among them.

Of course, later in the epidemic, AIDS appeared in gay men who did not have this history of multiple sexually transmitted infections, and such men might have been first seen by physicians who were beginning to specialize in the treatment of this new condition.

The physicians taking care of the earliest patients would be experienced in treating diseases more frequently seen in a subset of gay men living in large US cities; in effect, this kind of practice constituted a medical sub-speciality. In the early 1980s this did not include a familiarity with the characteristic opportunistic infections of AIDS, although in later years these physicians would become experts in this field. But in the first 3-4 years of the epidemic they would most probably have only started to become familiar with PCP, and concerned mainly with the diagnosis and treatment of this condition, rather than its prevention. Perhaps in the early years of the epidemic, some of these physicians who were aware of the means to prevent PCP were hindered by liability concerns in the absence of official guidelines. However, it cannot even be assumed that the physicians

providing care to the first patients would necessarily be aware, at that time, of the possibility of PCP prophylaxis Diseases of the immunocompromized patient were then, and in its broadest sense still remain a sub- speciality of infectious diseases practice, and the opportunistic infections were then best understood by infectious diseases specialists. The fact that this rather esoteric branch of clinical medicine had entered the territory of those physicians caring for the first AIDS patients made it critical that they receive some guidance from those familiar with this sub-speciality.
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The two sources from which such expert assistance might have derived were the infectious diseases specialist community, and more importantly, the Federal medical leadership that arose to specifically deal with this new condition.

The infectious diseases specialists were of course familiar with the diseases of the immunocompromised host, and certainly were knowledgeable about and interested in PCP prophylaxis. There were even some early studies including trials of a medication, fansidar related to bactrim. However, there is no formal structure by which their expert advice might have been communicated to those physicians taking care of the first patients. These physicians as noted would soon become experts themselves, but in the early days PCP would be far from their experience.
If in the early years, any advice on the importance of PCP prophylaxis did originate from the infectious diseases community, to individual physicians, it was certainly not heeded.

I had been attached to this community in New York City since the mid 1970s, having worked in the infectious diseases section of the Department of Medicine at the State University of New York (Downstate). I even first heard about the possibility of a new disease in homosexual men as early as 1979, at the regular Monday afternoon meetings, called the intercity rounds, held at different New York City hospitals by the infectious diseases specialists. I was thus in a rather unique situation as a person trained in clinical infectious diseases and microbiology, and also among those physicians seeing the first patients. My own early use of bactrim or dapsone, another effective prophylactic agent, was disapproved of. I was not alone in this practice which became more common, at least in New York City, before the 1989 recommendations.

It is of course possible that some initiative might have been displayed by a respected organization in creating a framework where PCP prophylaxis might have been discussed and the issue brought to wider attention. In this respect I was at fault for not promptly suggesting this to the AIDS Medical Foundation (later to be known as AmFar) when I was its scientific director. I did, without success, suggest such a meeting on PCP prophylaxis after I had left this organization.

It is not unreasonable to expect that it is the responsibility of government health officials, whether State or Federal, or even local, to define priorities in health care. Of course they do this, but in the case of PCP prophylaxis, the very long delay in addressing this problem had lethal consequences

The infectious diseases community certainly did demonstrate an interest in PCP prophylaxis in contrast to the total neglect displayed by the leadership of the Federal response. But it was left to the community of people with AIDS to finally demonstrate that PCP prophylaxis could be effective in AIDS. It bears repetition to point out that there really was no need to even subject patients to this exercise with pentamidine, which really was a response to the neglect of bactrim by the Public health Service. No reason had ever been advanced to suggest that bactrim prophylaxis would be less effective in AIDS than in other conditions. Studies on toxicity management and optimal dosage pf bactrim would of course have been appropriate.

The long and tortuous road to PCP prophylaxis was therefore completely unnecessary, and can be attributed, at least in part, to a failure of scientific and medical leadership. The practice of medicine tends to be conservative, with a reluctance to prescribe treatments that have not been recommended or approved by some recognized authority. The medical leadership spoken of above relates to this authority. This concept of medical leadership which although quite real, is difficult to define. Perhaps it may be described by the following example: If a physician is accused of malpractice he or she could probably successfully defend themselves by claiming that the practice in question was recommended by certain authorities (such as a set of NIH guidelines, CDC recommendations, a panel of the American College of Physicians, or Harrisons or some other respected text book of Medicine), but not by authorities such as holistic or some other alternative medicine expert , or by experts without affiliation to a respected institution. Special respect is given to Federal health authorities such as CDC, NIH and of course FDA which can impose its dictates directly by law. By this example the medical leadership entities referred to would be those whose advice is regarded as authoritative.

The CDC was of course engaged in the epidemic from its start; as the only source of pentamidine, used to treat PCP, the CDC became aware of the increased number of requests for this medication and in this way knew that PCP had become more prevalent. It was the CDC that first brought attention to the epidemic through its morbidity and mortality weekly reports, and rapidly conducted the first epidemiological investigations. However, they remained silent on the issue of PCP prophylaxis until recommendations appeared in 1989. The particular nature of the leadership that did develop at the NIH may also have played a role. Dr Fauci who could be regarded as the head of the NIH medical and scientific response, was not known as an infectious diseases expert. But such experts were surely part of his team. One can only assume that their long silence was related to toxicity concerns with the use of bactrim, but if so, there certainly was no hurry in addressing these concerns. They were finally overcome, and prophylaxis with bactrim is now the standard of care. Because of their long delay in dealing with this concern, one cannot ignore the possibility of some indifference to the plight of people with AIDS. Such was the influence of the NIH leadership in defining priorities that AIDS activists did not take up the issue of PCP prophylaxis until about 1987. This appeared to be mostly, but not exclusively in the context of clinical trials, and with a focus on aerosolized pentamidine rather than bactrim. In mitigation, it must be noted that AIDS treatment advocacy started to become organized only in 1987.

Individuals, such as Michael Callen had been trying to bring attention to PCP prophylaxis long before this, but without success. But he was in a rather exceptional position of having an independent infectious diseases expert as his physician and collaborator. As odd as it may appear I believe he was almost alone in these early efforts. I had told him about studies on the use of bactrim for PCP prophylaxis and given him material to read. My own early efforts, as a physician were also to no avail but a short article I wrote for a patient newsletter, the PWA Coalition Newsline, in 1987, entitled "No one should get PCP a second time" [viii] might have alerted some. The indifference to these independent efforts is a further example of the considerable influence of the Federal leadership in defining treatment and research priorities.

It might have been expected that at least secondary PCP prophylaxis would have been an obvious issue to be taken up by AIDS activists very early in the epidemic.
But as noted, it was only in the late 1980s that the objectives of AIDS activism were extended to include issues related to treatment and research.
In the early years, in so far as AIDS activism had taken an active role in treatment and research issues, it probably had little or no effect in accelerating the introduction of PCP prophylaxis.

.Turning now to the question of whether the fact that the first patients were gay men or intravenous drug users influenced the medical and scientific response to AIDS and so perhaps indirectly, contributed to the delay in issuing recommendations for PCP prophylaxis.

The major groups suffering from AIDS in the US are still not entirely free from discriminatory practices against them, and it is not beyond conjecture that this may be reflected in the responses to health emergencies affecting them. Responses might not be equally expeditious and of comparable competence when the emergency affects different groups. Science and medicine do not operate in a social vacuum and one might expect that on many levels, the nature of the medical and scientific responses will, in different and sometimes opposing ways, reflect societal prejudices.
In Man Adapting, Rene Dubos notes that:
"The presuppositions on which medicine operates are thus conditioned by the general philosophy of the social group as a whole" and adds the words of Oliver Wendell Holmes in 1860:
"The truth is that medicine, professedly founded on observation, is as sensitive to outside influences, political, religious, philosophical, imaginative, as is the barometer to the changes in atmospheric density"

This is evident when considering groups that are defined on the basis of sexual orientation. This is something that Michael Callen took into account, and who remained without support on the issue of PCP prophylaxis by a community which seemed to place

its trust in the established authorities. Authorities we have seen who had neither the compassion nor competence to at the very least, expeditiously clarify toxicity and dosage concerns related to the prophylactic use of bactrim, and thus have prevented tens of thousands of deaths from PCP, which in its effects, are deaths by suffocation.

With regard to homosexual men, there was an interesting and completely irrational medical development in the late 1970s that very aptly illustrates the comments of Rene Dubos and Oliver Wendell Holmes quoted above. This was the medicalization of male homosexuality, not in the sense that sexual orientation itself was of medical interest, but rather that there were medical consequences of male homosexuality, as a generalization, without qualifying the specific situations when such medical consequences might be seen. This would be equivalent to stating that there are medical consequences to heterosexuality, (or even to life itself) rather than stating that in certain specific situations, sexual contact of any kind might have medical consequences. .

Even before the start of the epidemic, disease in homosexual men was becoming a sub speciality in itself. There were numerous articles and even books devoted to the medical hazards of male homosexuality. . This specialization was taken to absurd lengths, so that in New York City, intestinal parasitic diseases were declared by the Health Department to be a sexually transmitted disease among gay men. That such infections can be sexually transmitted is of course nothing new; this is obviously the case with all infections more frequently transmitted by contaminated food or water. This obvious fact was lost in the zeal to create this new medical sub-speciality.
That a sexual mode of transmission of such infections should be confined to homosexual men was an absurd and dangerous contention. Women who had not travelled to endemic areas had great difficulty in obtaining a diagnosis of intestinal parasitic disease. I had treated such a woman who had found her way to my practice after reading about .this new hazard to the health of homosexual men. She told me that she engaged in the same practices with her male partner, which spread the infection in gay men. As a result of her suspicions it was possible to rapidly bring an end to almost two years of sometimes invasive, but always unsuccessful attempts to find the diagnosis of an easily treatable disease.

This is one unfortunate result of attributing a risk for infection to sexual orientation, rather than to specific sexual practices, practices that may be shared by women and heterosexual men. This irrational approach can only be attributed to the fact that physicians, even those who themselves are gay, are not exempt from influence by prevailing social attitudes.

Yet another example of the attribution of distinct medical pathologies to gay men was the common diagnosis made in large US cities at that time of the “gay bowel syndrome”. Not only is this term totally resistant to rational definition, its designation assumes that all homosexual men are at risk from this mysterious affliction

It should be emphasized that when these various pathologies are said to be characteristic of homosexual men, without qualification, this is in effect stating that homosexuality

itself carries the risk of disease. This dangerous conclusion largely escaped notice in the US during the late 1970s when this view of male homosexuality was being advanced. As already noted, it is a mistake to attribute risk for disease to sexual orientation, rather than to specific sexual practices, and the circumstances under which they occur. It is also a mistake to assume that sexual practices, their specific nature, when and where they occur, and the choices made regarding the nature, frequency and diversity of sexual contacts will be uniform amongst homosexual men, or for that matter, among heterosexual men and women..

That such generalizations are indeed made is exemplified by a CDC report in the early 1980s on AIDS causation[ix] which, because its conclusions were influential and often cited, will be described at greater length. This report proudly proclaimed that after an intensive investigation of a cluster of AIDS cases in Los Angeles, a transmissible agent was deemed to be responsible for the disease. This was deduced from the finding that members of this cluster could be connected by indirect sexual contact among them. It was argued by the CDC that since a gay man of an age range when sexual activity can be presumed, has contact with 12.5 different partners a year!,[x] and given the male population of the appropriate age range in the area in question, and the proportion (derived from Kinsey) who were gay, random contact amongst such a group resulting in the acquisition of AIDS could only mean that a transmissible agent was responsible. This example is given at some length, as it not only illustrates the absurdity of regarding gay men as a homogenous group, but is also a discouraging example of the calibre of some government research, as well as demonstrating how social attitudes can permeate scientific observation.

The most likely explanation of this cluster of AIDS cases in California, is that it included a relatively small subset of gay men with a similar life style, frequenting the same establishments and thus contact between them was not at all unlikely. It was certainly far from random.

Of course these specific examples did not directly retard the introduction of PCP prophylaxis. They do however illustrate that ignorance, prejudice and incompetence were not incompatible with research into this new disease by an agency of the US Public Health Service. An agency moreover entrusted with formulating treatment recommendations. It is not an unreasonable conjecture that such ignorance and prejudice could influence rational approaches to dealing with a health emergency involving homosexual men, and thus indirectly contribute to a view that did not see the provision of secondary PCP prophylaxis as an urgent issue.

In summary, it seems clear that the delay in the introduction of an obvious life saving, or more realistically, in the 1980s, life extending, measure resulted from a combination of influences. There was an insecure and still developing scientific and medical leadership, which in its lack of vision and competence, relied on a poor perception of the principles that should provide guidance when confronted with clinical uncertainty. The considerable delay in conducting a trial of bactrim prophylaxis can only be attributed to indifference, incompetence, or both. That such a trial was even necessary is arguable. One might

reasonably accept that the nature of the groups primarily affected played a role in influencing this lethal inaction. In the early years, those who claimed to represent the interests of infected individuals were notably silent regarding the urgency of providing recommendations for PCP prophylaxis, expressing concern only one to two years before the recommendations were finally issued. Once again, the exception here was Michael Callen, who was tireless in his demands that recommendations for PCP prophylaxis be put into place. What is clear is that there was no persistent and vociferous demand for PCP prophylaxis.

One must fear that this is not an isolated example. Despite the tremendous advances that have been made in the treatment of AIDS, we are far from being able to claim complete success. There are probably several potentially productive research avenues that are being ignored for the same reasons responsible for the prolonged neglect of PCP prophylaxis.

Addendum

The following are excerpts from the 1989 CDC recommendations for PCP prophylaxis. They also deal with preventing a first episode of PCP (primary prophylaxis), but the recommendation regarding trimethoprim-sulfamethoxazole (bactrim) to prevent a recurrence of PCP (secondary prophylaxis) could have been issued in 1983. The superiority of bactrim over pentamidine is also noted.

. The recommendations state that …… prophylaxis should be instituted when patients become immunologically susceptible to PCP……. The goal of this approach was to reduce the frequency both of initial episodes of PCP (primary prophylaxis) and of relapses or recurrences (secondary prophylaxis). Either oral trimethoprim-sulfamethoxazole (TMP-SMX) or aerosol pentamidine was recommended for prophylaxis, but because direct comparative data were lacking, neither regimen was endorsed as ``preferred.''

Since the recommendations were issued in 1989, additional information has become available about the efficacy and safety of aerosol pentamidine and oral TMP-SMX. A trial sponsored by the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group compared these two regimens in a prospective randomized study; in August 1991, this study was terminated by an independent data and safety monitoring board because statistically significantly fewer recurrences of PCP were observed in the oral TMP-SMX group than in the aerosol pentamidine group . On the basis of this finding and other studies assessing PCP prophylaxis, the Task Force was reconvened on October 5, 1991. This report contains the revised recommendations issued by the Task Force.

Before antipneumocystis prophylaxis was widely prescribed, most North American patients with acquired immunodeficiency syndrome (AIDS) ultimately had one or more episodes of Pneumocystis carinii pneumonia (PCP). These episodes often resulted in hospital admission and were associated with considerable morbidity, mortality, and cost.

During the 1980s, practitioners succeeded in decreasing the morbidity, mortality, and expense of these episodes by making earlier diagnoses, using outpatient oral or parenteral therapeutic regimens, continuing therapy more aggressively despite mild toxicity, using alternatives to sulfa-containing regimens (e.g., trimethoprim plus dapsone), and using corticosteroids as initial adjunctive therapy for severe disease.. Despite these advances, PCP continues to be a serious problem for human immunodeficiency virus (HIV)-infected patients, and prevention of cases continues to be an important goal.

The recommendations do acknowledge the work of Walter Hughes in providing evidence in 1977, that bactrim could prevent PCP in leukemic children. In fact Walter Hughes was a member of this expert panel. An AIDS patient was also a member of this panel, and apart from this individual, members of the panel were experts in the field of PCP and have never explained their long silence on secondary prophylaxis, despite their knowledge of the means to achieve this and their recognition of the gravity of the problem. Of course this most probably, has never been asked of them, which is itself part of the difficulty one faces in attempting to define the forces that shaped the response to this public health emergency.

[i] Michael Callen. Surviving AIDS Harper&Collins p24

[ii] CDC. Guidelines for prophylaxis against Pneumocystis carinii pneumonia for persons infected with human immunodeficiency virus. MMWR 1989;38(No. S-5):1-9.

[iii] ACRIA Update summer 2001 Vol 10 No 3 Richard Jeffries

[iv] Hughes WT, Kuhn S, Chaudhary S, et al. Successful chemoprophylaxis for Pneumocystis carinii pneumonitis. N Engl J Med 1977;297:1419-26.

[v] In Infection and the Compromised Host. 1981. James C Allen, Ed. Pneonucystis carinii pneumonia, Walter T Hughes p91 Williams and Wilkins

[vi] Wormser GP, Horowitz HW, Duncanson FP, et al. Low-dose intermittent trimethoprim-sulfamethoxazole for prevention of Pneumocystis carinii pneumonia in patients with human immunodeficiency virus infection. Arch Intern Med 1991;151:688-92.

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[vii] Fischl MA, Dickinson GM, LaVoie L: Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for Pneumocystis carinii pneumonia. JAMA 259:1185-89, 1998.

[viii] PWA Newsline, No one should get PCP a second time, JASonnabend. Reproduced in Surviving and Thiving wih AIDS 1987, with minor changes by Michael Callen..

[ix] CDC MMWR 1982 July 9;31:353-61

[x] Derived from a survey conducted by a pornographic magazine!.

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