Biotherapy 9: 17–26, 1996.

AIDS and transfer factor: Myths, certainties and realities

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Key words: AIDS, cancer, cell mediated immunity, cytotoxic T- lymphocytes, HIV, normal science, transfer factor, vaccines

Abstract

At the end of the 20th century, the triumph of biology is as indisputable as that of physics was at the end of the 19th century, and so is the might of the inductive thought. Virtually all diseases have been seemingly conquered and HIV, the cause of AIDS, has been fully described ten years after the onset of the epidemic. However, the triumph of biological science is far from being complete. The toll of several diseases, such as cancer, continues to rise and the pathogenesis of AIDS remains elusive.

In the realm of inductive science, the dominant paradigm can seldom be challenged in a frontal attack, especially when it is apparently successful, and only what Kuhn calls "scientific revolutions" can overthrow it. Thus, it is hardly surprising that the concept of transfer factor is considered with contempt, and the existence of the moiety improbable: over forty years after the introduction of the concept, not only its molecular structure remains unknown, but also its putative mode of action contravenes dogmas of both immunology and molecular biology. And when facts challenge established dogmas, be in religion, philosophy or science, they must be suppressed. Thus, results of heterodox research become henceforth nisi – i.e., valid unless cause is shown for rescinding them, because they challenge the prevalent paradigm. However, when observations pertain to lethal disorders, their suppression in the name of dogmas may become criminal. Because of the failure of medical science to manage the AIDS pandemic, transfer factor, which has been successfully used for treating or preventing viral infections, may today overcome a priori prejudice and rejection more swiftly. In science, as in life, certainties always end up by dying, and Copernicus' vision by replacing that of Ptolemy.

Abbreviations: CMI = cell-mediated immunity; CTL = cytotoxic T-lymphocytes; HIV = human immunodeficiency virus, HSV = herpes simplex virus; MuLV = murine leukaemia virus; SIV = simian immunodeficiency virus; VZV = varicella zoster virus.

The syndrome or the virus

Examining certain aspects of science policies and politics, leading to conceptual obstructions, is not a pure philosophical or idle intellectual exercise. Indeed, sometimes deadly diseases are involved, and AIDS offers a timely example.

Despite the identification of HIV, the causative agent of AIDS, only three years after the onset of the epidemic and its near complete dissection today, the pathogenesis of the syndrome is still not understood, the therapeutic approach remains ineffective, and the clinical results totally disappointing. A hiatus between knowledge and clinical results is becoming apparent and the gap widens with time. However, despite the therapeutic failure, only those leads within the dominant stream of thought are explored. Thus, for over a decade, neither the fact that some patients are able to resist infection [1], nor encouraging preliminary results, reported as early as 1987, using transfer factor for the treatment of AIDS [2], have drawn the attention of the investigators, the funding agencies and research policy makers, who apparently cannot see the disease for the virus.

Discordance between the quantity of available analytical data and solutions requiring a synthetic approach, as well as deliberate disregard of facts or ideas, is more common than expected in science, especially in biomedical disciplines. The failure in treating AIDS, after that in controlling cancer, is an illustration

of a dominant trait of "normal science" [3]: results are never proportional to the amount of knowledge gathered by accretion, following the rules of inductive research.

The kernel of my contention here is that existing funding could produce far more significant results if it were partially used to finance *extraordinary science* [3, 4]. To substantiate this assertion, I shall review some aspects of AIDS research and discuss why certain facts, and seemingly rational approaches are at times neglected, whilst cul-de-sacs may be investigated with unmitigated ardour. In this context, censorship, i.e., selective consideration of facts and ideas — a natural constituent of normal science — becomes a decisive factor in transforming research into a closed system. Transfer factor may be cited as a typical example of an a posteriori factual rejection, i.e., rejection of established facts when ossification of the consensual thought does not allow for their existence.

Normal science as religion

Thomas Kuhn has called science carried out routinely and not challenging the paradigm, "normal science" [3, 4]. Despite disagreements among philosophers, by and large, *normal research* proceeds by induction; it is a linear process of collecting and comparing factual observations, increasing knowledge by accretion. Today's biological research closely follows the kuhnian model, and the fact that both Kuhn and Popper condemn progress by accretion, does not change reality [3–9]. Cancer research, and more recently the human genome project, are examples of a mere collection of observations by skilled technicians, where the construction of new, daring, falsifiable hypotheses is deemed unnecessary for achieving progress.

Normal science is organized around central hypotheses which have evolved to consensual truths or paradigms, and the majority of scientists are transformed into their hidebound guardians. Such a system is gradually closed, becoming quasi-impermeable to outside reality, the belief in the perfection of its dogmas being its defense against the challenge of unwelcome conjectures, and even observations. Many barriers protect the citadel. Peer review committees of gatekeepers are created to make certain that the rules are respected and that heretics do not find their way to the core of the system to challenge the existing order from within; support is offered for projects within the dominant paradigm, and publications will be screened for their conformity to it; funding in turn will be reserved for those who can prevail with a high number of printed reports supporting the paradigm. The outcome of this policy has been described as the Saint Matthew effect [10].

The consequence of this policy is that the number of paradigmatic publications cannot but increase, whereas the risk of printing controversies cannot but decrease, to the utter satisfaction of the control bodies and funding agencies: all approaches being within the limits of the accepted tenets, no major controversial observations or errors would easily appear, but neither would unexpected discoveries. By introducing the "impact factor", which was supposed to measure the penetration of a publication in the scientific community by the number of its citations, Eugene Garfield produced a tool for identifying and measuring an important aspect of normal science [11]. Gradually, with time, it became a means to increase the closure of the system and the effectiveness of the gatekeepers. Thus, only observations within the limits of the existing thought would be readily published in high impact journals, read, consensually appraised, and subsequently acquire a high impact. The Vatican's imprimatur, although lacking today's computer power, was just as efficient in preventing the diffusion of heretical ideas and in enforcing orthodox beliefs.

This type of science is far from the idealistic, close to myth description of Sir Karl Popper, who believes that science progresses through conjectures and refutations, and that each hypothesis, being by definition falsifiable, should be repeatedly tested until proven false and replaced [7-9]. Nearer to reality, Kuhn contends that the paradigm is overthrown only in exceptional circumstances of "essential tension" – when the gap between reality and belief becomes untenable — leading to a *scientific revolution* [3–6].

In his attempt to condemn the concept of normal science, Watkins accurately describes it: normal scientists are "under some mysterious compulsion to preserve the current theories against awkward results. Close examination shows that those theories lose their scientific status and degenerate into something like metaphysical doctrines"; thus, scientific normalcy amounts to "a closed society of closed minds" [12]. The reasons for such behaviour producing this state of affairs, although fascinating, are study matter for disciplines such as psychology and sociology. Suffice to say that scientists, even when medically qualified, are not psychologically better prepared to deal

with reality and social issues than politicians, the military, or the clergy.

Be that as it may, it is obvious that it is always more comfortable to dwell in certainty than in doubt — religion was invented for this purpose — and that certainty is not only the apanage of passion, it also often associates with reason. Resistance to change, in this case of the consensual framework, is a natural tendency and one way of averting or delaying *essential tensions* and *revolutions*. More often than not, it is achieved by unconscious and subtle manipulation of facts and ideas, a bona fide adaptation of new observations to existing theories. The ptolemaic system is a classical example. Thus, until Copernicus, Ptolemy's coherent construction remained valid and operational after the introduction of ad hoc corrections — epicycles on epicycles on deferents — to account for new, challenging the system observations. So, the system remained functional, despite the falsity of the underlying model, that of geocentricism [6].

When this method is not successful, i.e., when adaptations of the conceptual framework are not sufficient to integrate the challenging observations, facts may be discredited and discarded as observational errors. Barbara McClintock's observations on the "jumping genes", contravening the entrenched idea of genome's stability, were considered ludicrous for years, before receiving the recognition of the Nobel prize Committee [13].

In their struggle for power, via dogmas, followers and opponents of the paradigm may resort to fraud, faking or misappropriating experimental evidence. The controversy over a potential Nobel prize for discovery of the AIDS virus is a recent example of blatant fraud, which despite wide publicity, had no consequences on the culprits' careers. In contrast, in the 70's, the fraud of a Nobel prize-candidate's assistant, who, under extreme pressure to produce results resorted to the use of paint to prove successful allogeneic mouse skin grafts, destroyed both careers [14]. Scientists, wooing peers' approval rather than solely embracing reality, are not immune to passion, nor to the lures of power; rather, they tend to succumb too easily to both.

Not only are scientific beliefs in our era substitutes for religious dogmas, but the underlying mechanisms of their formation and survival seem similar. When the Church had the power to censor scientific observation, the latter could not evolve outside the Aristotelian framework. However, when censorship became insufficient to secure stability and survival of the credos, like the henchmen of an endangered scientific tenet, the clergy tried to preserve the dogmas by adapting them to the scientific reality. But before accepting change, the temptation has always been to negate reality. The creationists' present struggle to save their faith in the biblical myths may seem ludicrous and contemptible, but in an analogous situation, pro-life supporters use murder to defend their beliefs, i.e., save life.

In theory, rejection of facts in science is condemnable on the grounds of objectivity and unbiased observation which, supposedly, govern research. In reality, observational filters are present at all levels and they do not pertain solely to marginal phenomena such as parapsychology. Although, even in such a case, even when the rejection of facts seems an appropriate measure for spooky topics, it is objectionable, since "it operates before considering the evidence". But "similar things happen constantly even where there is no suspicion of metaphysics. For instance, the theory of continental drift was long dismissed as unscientific, and so for a time were James Lovelock's suggestions about damage to the ozone layer" [15]. Lovelock's text is a fascinating illustration of a subconsciously programmed fact-rejection. "It is a scandal that the vast sums spent on expensive big science of satellite, balloon and aircraft measurement failed to predict or find the ozone hole. Worse than this, so sure were the computer programmers that they know all that mattered about the stratosphere, they programmed the instruments aboard the satellite, that observed atmospheric ozone from above, to reject data that were substantially different from the model predictions. The instruments saw the hole, but those in charge of the experiment ignored it, saying in effect, 'Don't bother us with facts; our model knows best'. The Ozone War is littered with stories of this kind of military incompetence" [16].

Obviously, operating in this fashion appears simpler, time and energy saving. Closer examination shows counterproductivity, contradiction with the system's fundamental premises of objectivity and obfuscation of the mind, which can lead to disaster.

It thus appears that the only distinction between a credible and a non-credible observation is whether or not it fits with the consensually accepted reality, not with the factual experimental data. Logically, when "confronted with the unexpected, the scientist must always do more research in order further to articulate his theory in the area that has just become problematic"; in fact though, "no exclusively logical criteria can entirely dictate the conclusion he must draw" [5]. In other words, irrational psychological impulses may inspire scientific conclusions and rejections. But as

soon as a phenomenon moves outside the boundaries of the accepted reality, it becomes marginal, comparable to metaphysical phenomenology, and subject to irrational treatment, e.g. to derision and rejection.

AIDS: A syndrome outside the paradigm

There are instances where factual rejection may have immediate disastrous consequences. For instance, rejection of the evidence for the infectious aetiology of AIDS for ten years would have resulted in an epidemiological catastrophe.

This is not pure speculation. It is plausible to imagine that Duesberg's arguments [17–20] might have prevailed for a few years, and that the role of HIV was relegated to that of a co-factor. Under this scenario, retroviral research funding would have been minimal, and diagnostic tests would not have been developed nor would educational efforts have been undertaken to prevent the spread of HIV. Thanks to transfusions of unscreened blood, the number of seropositives would be at par today with that of seronegatives.

The early history of unravelling the AIDS aetiology makes this scenario even more plausible. Indeed, the infectious aetiology of AIDS was called a "simplistic hypothesis" as late as 1984 [21], whilst, even to this day, Duesberg continues to claim the unimportance of HIV in the aetiopathology of the syndrome [17–20].

The hypotheses produced by respected scientists at the beginning of the AIDS epidemic, to account for its aetiology, negating the existence of a new infectious agent, were ingenious and – complex. They had to be, to remain viable and discount reality with some credibility [21–26]. Nonetheless, despite the scientific and medical community's lack of formal philosophical training, one may contend that it was not difficult to conceive and investigate the hypothesis of the existence of a new infectious agent as early as 1981. Instead, ignoring the rather recent teachings of Legionnaire's disease, the infectious hypothesis was discarded with vehemence.

If from the beginning AIDS appeared strange, it was mainly because it was confined to certain groups: homosexuals, haemophiliacs, Haitians and heroin addicts. Homosexuals being the first and largest identified population, inductive thinking had to propose a plausible hypothesis compatible with observed facts and existing certainties. Formulating theories to incriminate homosexuality was certainly a complex task, but more within the realm of the known, and it benefited from the undercurrent support of the moral majority: incriminate what has been for other reasons condemned, was more comfortable and consensus-nurturing. Religious neurotics were quick to jump to the rescue of the untenable hypothesis, and to remind us that homosexuality was a behaviour condemned by the commands and the representatives of the Judeo-Christian God. Thus, AIDS became God's justification in the 80's, of his very early commandments [27].

The homosexual hypothesis was the first naive construction to account for the pathogenesis of AIDS. It was simple, obvious and it appeared correct, since in the early years, almost all known cases were homosexuals. As usual, when prima facie simplistic explanations are apparently flawless, logic recedes and it is easily forgotten that a phenomenon in biology can seldom receive a simple and univocal explanation. Interestingly, followers of the homosexual theory were not bothered by stumbling logical difficulties, the main one being that homosexual practices have always been present in human societies, but not AIDS. Thus, the attempt to account for the sudden outbreak of the epidemic in the 80's as a consequence of sperm's immunosuppressive properties should have seemed utterly preposterous. But proponents of the ludicrous hypothesis were stubborn, and adjustments were devised to save it. The existence of adjuvant factors was postulated, and recreational or hard drugs were proposed to that effect. The presence of the syndrome among the haemophiliacs was explained by the immunosuppressive properties of the blood by-products, whereas the high prevalence in Haitians was attributed to their homosexuality and/or drug addiction. The analogy with the adaptation of the ptolemaic system to the heliocentric reality is striking. But, errors of the past never become lessons for the present.

It may be significant that the homosexual explanation is not dead today, even among non-believers in revealed biblical truths, i.e., among scientists who still see the semen playing a major role in the pathogenesis of AIDS [28], whilst others [29] have decided to widen the argument and include additional factors, but exclude the HIV. When a seemingly successful research has not produced the expected tangible results — here a therapy — , it is tempting to seek the solution in the irrational collation of data rather than by exploring alternative new hypotheses.

The cancer blueprint

As a consequence of the failure to show significant clinical results, those who have vested interests in uttering statements of hope, have often suggested that the pattern of AIDS therapy will follow that of cancer, implying that it is unrealistic to expect the discovery of an antiviral capable of eradicating the HIV infection in the near future. Thus, a strategy using antiviral polychemotherapy should be developed which, after several randomized clinical trials, might eventually produce some long lasting effects.

Unfortunately, the analogy between AIDS and cancer is pertinent. Quasi–consensually, cancer has been accepted as the result of an irreversible malignant change in the normal cell. The alteration producing the malignant cell — be a mutation or a viral insertion being irreversible, it follows that the only evidently rational therapeutic strategy would be the eradication of the mutant cell and its progeny. Notwithstanding contradicting observations – several reports in the 60's and 70's had unequivocally challenged the irreversibility of the cancer cell dogma [30–32] – , these conjectures gradually became certainty determining the therapeutic methods, all aiming at the extermination of the tumour cell: surgery, radiotherapy, chemotherapy, immunotherapy. Refined with time, these techniques are the ones still in use today, with results far below the promises of politicians and scientists. Indeed, Nixon's cancer campaign, launched in 1971, made cancer a target to conquer in the 70's, as the moon was conquered in the 60's. The subsequent RFP (requests for proposals) programme launched by the NCI was supposed to ask scientists to produce the answers to the problems defined by the *thinking* elites of the paradigm. The apology of this "war" is summarized in a NCI publication, with a significant title: "Contrary to Nature"[33]. However ridiculous it may seem today, it is the explicit epitome of a credo, and an illustration of the absurdities that certainty can produce.

Despite claims of politicians and fund raisers, and the enormous research budgets, cancer mortality statistics look worst today than at the beginning of the century or 20 years ago [34]. But in normal research failure does not determine change swiftly. It is, nevertheless, candidly admitted that "the main conclusion we draw is that after 35 years, the intense efforts to improving treatments [for cancer] must be judged a qualified failure ... we are losing the war against cancer" [35]. Obviously, such statements have no effect on the cancer paradigm and the underlying policies which will continue unswayed until its death, but make R. Gallo's assertions that "AIDS is following almost too neatly the history of cancer chemotherapy, and one could almost predict exactly what will happen next", seem piteous and asinine, if not cynical. Cancer is an illustration, a forcible example of predictable and predicted failure of research confined within the boundaries of consensual paradigmatic certainties [36]. It is reminiscent of what is happening with AIDS: the scientists' and politicians' boastful claims [e.g., 37, 38] and, several years later, the paucity of results.

AIDS and cancer seem to have something fundamental in common indeed: they share the same conceptual errors – i.e., facts ignored to save theories. And the results are comparable: failure to produce tangible clinical results. It is thus ironical, and it would be cynical, if it were not pathetic, to present as promising the fact that the pattern of AIDS treatment will follow that of cancer.

Transfer factor a concept outside the paradigm

The evolution of transfer factor's perception by the scientific community, has followed a rather unusual career. Here, previously accepted facts are not rejected because they are refuted by new experimental evidence, or alternative explanations are offered, but simply discarded, deliberately placed into oblivion. Forty five years after its existence has been postulated, because its structure remains elusive and its putative mode of action apparently does not fit within the boundaries of the current certainties of immunology and molecular biology, it has been implicitly decided by steeped-in-orthodoxy guardians, to do away with the concept, together with the underlying supportive evidence, by ignoring them. Consequently, over 1200 reports printed in the past twenty five years [39] should be scraped, not because an alternative explanation to the described observations can be proposed, but precisely because none seems adequate to account for them.

The implicit negation of transfer factor's existence may be a mirror image to the previous proposed scenario of refuting the AIDS infectious aetiology for a decade. But this time the setting is real: all research on the subject has been stifled and funding dried up. However, continuing the analogy with the non-viral aetiology of AIDS, if the preliminary results reported on the use of transfer factor in AIDS were to be confirmed, the consequences of deliberately ignoring not

only theoretical considerations, but also factual evidence, could prove to be as catastrophic as ignoring the evidence for HIV for ten years, and as criminal as dispatching for commercial reasons contaminated blood by-products to haemophiliacs. One can imagine what adequately funded research would have produced since 1987 (the first data using transfer factor in HIV infected patients were published that year [2, 40]), and the toll that patients had to pay because of the deliberate decision not to explore this therapeutic approach.

Transfer factor's rejection is, in certain aspects, reminiscent of that of DMSO. Because it was empirically utilized for the treatment of miscellaneous and unrelated pathological conditions (from eczema to arthritis, and from burns to psoriasis or to mental disorders), based on unsubstantiated rumours of toxicity, the FDA decided to ban its medical use. It is true that reductionist thought profoundly dislikes compounds with pleiotropic effects. Thus, research on the molecule withered, notwithstanding its extraordinary properties on cell differentiation [e.g., 41–44], while the toxicity issue remains unresolved to this day, despite its use for cryopreservation of embryos, tissues or cells injectable into patients. A recent report indicates that after a decade of procrastination, NIH experts accepted the product's lack of carcinogenicity, albeit no study has shown that the non-toxicity *impression* was any more valid than that of toxicity [45]. Rumours versus rumours. Once again we are closer to religious beliefs than to scientific objectivity. Such irresponsible attitudes - often tolerated by the editors of the scientific press - are common and indicative of the role that lack of courage plays today. For it is always safer to say *no*, and there are no sanctions against procrastination or refusal. A behaviour described by Samuel Butler in 1872: "...it seemed to be counted the perfection of scholarship and good breeding among them not to have - much less to express - an opinion on any subject on which it might prove later that they had been mistaken. The art of sitting gracefully on the fence has never been brought to greater perfection than at the Erewhonian Colleges of Unreason..." [46].

Under the crack of reality

Despite the early discovery of its causative virus, the pathogenesis of AIDS is still not understood. Inter alia, the pace of progression to the full blown syndrome varies from one patient to another, but it is unclear whether the preponderant role should be attributed to the changing virulence of the various viral strains, to individual differences of the immune system, or to co-factors, e.g. other viruses and microorganisms. What seems certain is that cell mediated immunity (CMI), as in most viral diseases, plays a key role in the progression of the HIV infection. However, one had to wait until 1992 for clear prompts that attention should be shifted to the immune system [47]. It was the time when the failure of the research, so far focused on the description of the virus, to produce clinical results became obvious and inspired eloquent editorials, inviting scientists to remember that uncertainty is always present in our world [48].

Because the success of virology, associated with that of molecular biology, in identifying the virus has been remarkable; because it made intuitive sense that antivirals preventing viral replication should curtail the CD4 cell loss; because the evolution of a viral disease is, we used to think, well understood and cure is synonymous with viral elimination, it seemed logical, and it is still intellectually tempting to many, to believe that the solution lies in the discovery of the miraculous antiviral compound.

Be that as it may, it now seems univocal that CMI is responsible for the observed resistance to disease progression [49–53] and in certain cases to infection [54–57]. Albeit known antivirals, potent in vitro, fail to cure and antibodies to protect, these observations should be sufficient to suggest that the HIV infection is not outside the realm of our repertoire of the known, even if it does not fit within the ad hoc framework we have created for it. Indeed, herpes patients, for instance, suffer relapses despite the presence of anti-HSV antibodies, the defect lying in the CMI arm of their immune system [58–60]; once this is corrected, relapses subside [61–62], whilst mice can be protected from lethal HSV infection by specific transfer factor [63]. It is thus hardly surprising that all attempts to produce anti-HSV vaccines have failed since they were soliciting the B cell compartment of the immune system [64–72].

That anti-viral antibodies may in certain cases remain ineffective, and that CMI mechanisms may be efficacious is, therefore, in no way novel, unusual or specific to HIV infection. Rather, what is astonishing is the enormous effort stubbornly deployed to manufacture a vaccine addressing humoral immunity, despite past experience and repetitive failures to produce a herpes vaccine, and notwithstanding the evidence that the presence of anti-HIV antibodies does not abate AIDS progression. This enterprise continues uncurtailed, in

spite of the recurrent failures to produce results [73, 74].

The evidence for the role of CMI in the control of AIDS is as overwhelming as the failure of humoral immunity to neutralize the virus. Recent reports have substantiated this contention, suggesting a plausible mechanism: HIV-specific cytotoxic T-lymphocytes (CTL) would be responsible for controlling the infection [54–57]. Several observations favour this view. The presence of HIV-specific CTL in the blood of an uninfected child, born to an infected mother, implies successful resistance mechanisms induced by contact with the virus [54], as does the presence of HIV-specific CTL in seronegative partners of HIV-infected individuals [55]. These findings not only offer a plausible mechanism for the resistance to the disease, but also suggest that certain individuals, who have developed cellular immunity to HIV, are able to prevent infection and destroy the virus with such speed and efficiency that no antibody formation takes place [56], whereas others are capable of resisting progression of the infection [53] or even of clearing the infection and eventually becoming seronegative [57]. Rowland-Jones et al. reported that certain prostitutes, daily exposed to the virus, remain uninfected, as shown both serologically and by PCR, but they do develop HIV-specific CTL [56]. One major implication of this observation is that CMI, contrary to neutralizing antibodies, may protect against several viral strains: the Gambian prostitutes seem to be resistant to all HIV strains presented by their clients. Yet, the existence of uninfected homosexual or heterosexual partners of HIV-infected individuals has been known for many years. But as long as the failure of the consensual solution i.e., the use of neutralizing antibodies to combat the virus was not recognized, the CMI track was left unexplored.

Transfer factor acts on CMI, and it is known to be efficacious in treating viral infections. Indeed, CMI plays a key role in controlling such infections [61–63,73–78]. Observations, using HIV or SIV-specific transfer factor, have provided insights leading to the formulation of similar hypotheses: the possibility for CMI, probably via the CTL subpopulation, to control lentiviral infections. Indeed, a monkey model provided evidence that SIV-specific transfer factor can hinder disease progression and, furthermore, that transfer factor extracted from CD8 cells is the most potent [79]. More recent studies by Clerici et al. corroborated these observations: low dose, below threshold seroconversion level, SIV injections induce a T-cell mediated response capable of conferring resistance to subsequent virus challenge in macaques. And the authors contend that "AIDS vaccines should be designed to optimize the cellular arm of the immune response" [80].

The fact that transfer factor may induce cytotoxic lymphocytes is not new: it was reported twenty years ago [81]. This observation, together with the above cited evidence that CTL may be able to control the HIV infection, and the first encouraging data from the transfer factor use in AIDS, should have prompted an active investigation; but did not. Only recently has CMI received serious consideration for inclusion into the AIDS management paradigm, whereas transfer factor is still ostracised and remains off limits of the orthodox territory.

Yet, in several instances, transfer factor has been used not only for treatment, but also for prophylaxis against viral infections. Steele et al. utilized a VZV-specific transfer factor to protect leukaemic children from varicella infection [82]. Our own studies with a HSV mouse model have also shown that HSV-specific transfer factor, injected prior to a lethal HSV-challenge, has a prophylactic effect [63]. Since animal models, using the HSV or the MuLV in mice, or the SIV in macaques, are relatively inexpensive and simple to operate, this crucial issue, viz. the possibility of employing specific transfer factor to prevent viral infections, could easily be investigated. A vaccine, based on an oral administration of specific transfer factor, would be the simplest, least expensive and least toxic type of vaccine known to date.

Prospectives

Criticizing a posteriori contentions and certainties, when facts have proven them mistaken, might seem presumptuous and the exercise futile, if it were not in the hope to draw some insights and lessons for the future. Indeed, *retropredictions* i.e., predictions explaining the evolution of the past, are easy: retrospectively, reality always makes sense and more often than not facts become predictable; but "predictions are difficult, especially if they concern the future" [83]. Nonetheless, I shall try to make a few; they are always easier when they do not intend to flatter or to fool. Thus, the gloomy forecasts, foretelling the failure of inductive research to swiftly solve the cancer problem and reduce mortality, were proven correct fifteen years later [36, 84].

Imagining in 1995 strategies for coping with the HIV infection is not an extremely hazardous enterprise. The humoral vaccine track seems to be an impasse, whereas prophylactic vaccines based on CMI stimulation, viz. specific CTL induction, should become reality in the years to come. Combination of antiviral polychemotherapy to reduce the viral load, with immunotherapy to boost CMI defences and eliminate the HIV-harbouring cells, seems a plausible approach, the most plausible. This type of intervention should be started as early as possible: the time of a quiescent asymptomatic phase reflecting the inactivity of a dormant virus, is a myth of the past. We now know that the immune system launches a paramount struggle against the virus from the beginning of the infection [85, 86] and it is precisely at this stage that the immune system is in dire need of help, and outside intervention will be the most efficacious. This strategy should significantly reduce mortality and morbidity

Predicting transfer factor's future is a different affair. It seems highly probable that it will have a favourable effect on the evolution of AIDS. In the absence of alternative efficacious therapies, it is plausible to predict that it will be used in association with antivirals for treating this syndrome. Hopefully, its preventative potential will also be investigated, and it is equally probable that the data will prove its effectiveness. Results obtained with the HIV infection should then re-focus attention on this challenging immunological oddity, and provide funding for further research to solve its biochemical and immunological riddle. It should, thus, be possible to associate a structure to the concept and a mode of action to the molecule.

No doubt, the use of transfer factor for the prevention of viral, parasitic and mycobacterial infections will then be the object of unbiased clinical investigation. For both prevention and therapy, the main advantages pleading for this compound are low cost of production, absence of toxicity and easy administration. For countries with limited technological and financial resources, plagued with viral and parasitic infections, these features are additional and important arguments pleading for its wide use.

If transfer factor contributes, as I predict with undeterred optimism, to the solution of the AIDS problem, it will prove its value even to its adversaries, and will unerringly solve its own problems. It should also advance the formulation of new paradigms to accommodate its mode of action. All this, encouraging as it may sound, will not change the structure and functioning of biomedical research. It is within the ken of predictability that a many-valued logic approach will not be acceptable, at least for another half century, in biology; and also that it is forlorn to hope for scientists to spontaneously evolve and follow precepts of an ideal approach to unbiased investigation and "search their minds beforehand to find out what they would like to be true or false, and having got that clear, constantly discount their natural tendency in that direction" [87]. Thus, biomedical science will continue to be *normal*, plagued with certainties and controlled by the guardians of orthodoxy, those who managed to acquire the power to command funding and printing, and who believe that some crank has written that "through purely logical thinking we can attain no knowledge whatsoever of the empirical world" [88].

The only way to counterbalance this depressing kuhnian vision, is to secure funding for alternative, popperian-style research. Only politicians could impose such a change with affirmative action, but there is little probability that an event of the sort will ever occur, not before it has been convincingly demonstrated that *alternative research* is not only intellectually more gratifying, but also able to produce answers faster, and not least, at lower costs.

It is possible that private initiative might support such alternative systems and succeed in proving a prediction made several years ago: if 20% of the research budget were used to finance alternative research, the results would be comparable to those obtained with the remaining 80% [84]. Until then, scientists opting against the consensual comfort must continue to fight established paradigms, as they used to fight religious creeds when the Church was mighty. However, their task today is far more arduous: instead of fighting evident irrational myths on the name of reason, they must fight on the name of reality rationally established certainties, which have degenerated into dogmas.

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