

Clifton Leaf:

asking the difficult questions

→ Marc Beishon

Clifton Leaf sparked a lively public debate with a hard-hitting cover story for *Fortune* magazine, which asserted that America's 'war on cancer' is being lost. He calls on the cancer research community to show stronger leadership, increased cooperation, better focus and, above all, greater honesty about its successes and its shortcomings.

Few people outside the US will have heard of journalist Clifton Leaf and his crusade to challenge the cancer establishment on its lack of progress since president Richard Nixon launched America's 'war on cancer' in 1971. Those who have seen his lengthy cover story in *Fortune* magazine in 2004 – in which he takes a first shot at exposing what he sees as a dysfunctional, indeed 'broken', cancer research system – may have dismissed it as a local dispute between a business writer and the mandarins in charge of American research budgets. That would be to miss some of the toughest questions yet asked of the cancer community, which have ramifications worldwide not only for basic science researchers, but also for clinicians, advocates, regulators and politicians.

After looking at the raw data – the 'balance sheet' of the American cancer world – as only a financial writer could, Leaf's initial rosy view of the 'bang per buck' the country was getting from its investment turned to outrage when he discovered the true story that mortality statistics were telling.

"I found there were two stories being told," he says. "One was the patients' story – often heroic and very moving, told through advocacy organisations

that were clamouring for more money to step up efforts to fight cancer. The other story came from the scientific echelons of cancer – that they had discovered the holy grail with targeted therapies and the genetic underpinnings of the disease. That's all I heard – and not that we were making little significant progress and were actually losing the war."

Leaf initially unpicked some of the issues he believes are undermining the research effort. He looked at why those wonder drugs widely hyped then – Avastin, Erbitux, Herceptin and even Glivec – were not going to make much of a dent in the mortality rates, and working back, how the research community is set up to tackle relatively small parts of the biology of cancer, expending most of its effort to catalogue ever smaller components of individual signalling pathways while paying little heed to the dynamic interplay between them. He found an emphasis on developing drugs that may hold up tumour progression but do not actually address metastasis, and asked why much more effort is not being placed on carcinogenesis, screening and prevention.

In doing so, he scratched the surface of the structures and vested interests that he sees as obscuring



LUIGI INNAMORATI

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the big picture, including the way research grants are awarded in the US, the methodology and regulations associated with clinical trials, and the ownership of intellectual property. In true investigative style, Leaf has since ‘followed the money’ to find out why these and other ‘establishment’ issues have led to what he sees as such poor outcomes.

The phrase he uses to summarise the situation – “All the incentives are misaligned with the goals” – sounds like business speak, but as he explains, the ultimate goal is defeating cancer – and it just will not happen as long as researchers are being directed down the wrong tracks.

Among the top concerns are intellectual property (IP) and the infrastructure in which researchers currently work. “We have let IP rules run amok and allowed ownership of even gene data, which has prevented much basic and clinical research from being done. And we have pushed drug costs up to astronomical levels – there is no reason why they should be so much more expensive than in the past, save for the IP rules. We are granting patents to universities for the knowledge gained from taxpayer-funded work. And they turn around and sell this knowledge exclusively to developers who, by virtue of their monopolies, rack up the prices.”

Leaf extends his point to information sharing across the board, noting an often glacial speed for new drugs and techniques to become widely used, and a cultural resistance in any case to new ideas among the medical community. In the US, he is struck by the lack of a national biospecimen network. “We have a plethora of freezers with millions of specimens but no way of knowing what’s inside of them.”

There is a project looking at such a national tumour network, led by the National Cancer Institute, but as Leaf adds, “It’s not getting the money or push it needs. We don’t really have centralised leadership in the US – the NCI has historically been more like a cash machine, doling out money to the comprehensive cancer centres and research institutions, and the cooperative groups that control the clinical

trials apparatus – this is where the real power lies. They are the plutocrats and are resistant to anything that will take away their power.

“It has shocked me that we don’t have the political will to force change in this culture. For all the people running miles and miles to raise money for cancer, we have not yet harnessed this human power into political will, and I find that amazing.”

Leaf’s critique so far has focused mainly on America, but of course nearly all involved with cancer abroad look to the US. No other country has as many top clinical and research centres, and if the NCI is coming in for some criticism, Europe has not even the germ of a cross-border institution that could be its rival, and European efforts are seen as even more fragmented. As Leaf adds, since 2004 he has travelled extensively both home and abroad, and it is clear that not only must the US reform its cancer infrastructure, it must also tackle its traditional insularity and collaborate much more widely internationally.

In short, Leaf is asking people in what he calls the ‘cancer culture’ to become much more honest about these shortcomings, from the true mortality statistics to the systemic dysfunctions. Indeed, if he has one watch word for the future it is ‘honesty’ – in the same way that the movers and shakers on Wall Street, the City of London and the other financial centres have had to confront deep flaws in public reporting and decision making – and are still having to do so – cancer will also need root and branch reform in reporting progress and investing wisely.

In researching the cancer culture, Leaf has made some extraordinary connections with people in the community, including the heads of the major cancer centres such as MD Anderson and Dana-Farber, directors of advocacy organisations such as Susan G Komen for the Cure, where he is now on the board, and most appositely, from his investigative standpoint, the visionary – even maverick – researchers and clinicians who he feels have shaped most progress in the cancer battle.

The momentum of all this analysis and advocacy has now totally changed Leaf's professional life. Last year he left *Fortune* to carry on his advocacy work full time, and to complete a book (with publisher Alfred A. Knopf), which the magazine had kindly given him a year's start to write. The book will be his major contribution to date on where we are in the cancer war, and he promises it will be no sterile rehash of the many political and structural issues he's uncovered so far, but rather a much more lively – and optimistic – story based on his many conversations with those he sees as contributing most.

Leaf is himself a cancer survivor, which outwardly has played little part in his arrival in the cancer world. He was diagnosed with Hodgkin's disease as a teenager in the 1970s and was cured thanks to a 'brutal' experimental protocol involving MOPP, the first combination of chemotherapy drugs to treat the condition successfully. Treated at the NCI by among others Bruce Chabner – now at Harvard and one of Leaf's insightful sources on the American research enterprise – he was subjected to a ping-pong regime of chemotherapy, alternating with radiotherapy, which caused much sickness but effected a cure, at the expense of his thyroid gland, removed after accidental irradiation.

"Undoubtedly, much progress has been made across many fronts, from nausea control to vastly improved cancer care, not least for children, to soci-

etal acceptance of the disease," says Leaf. "When I was treated it was after the Three Mile Island nuclear power plant accident – some of my schoolfriends were uneasy about coming near me."

But his own experience, and subsequent revisiting of how cancer has been tackled since then, does reveal a striking difference. "We were more willing to build up experimental knowledge quickly and inch forward – in the early history of childhood leukaemia there were rapid-fire protocols and little to get in the way such as review boards and other regulatory hurdles, and political turf battles between the cooperative groups that run clinical trials. It was more seat-of-the-pants experimenting rather than preoccupation with safety, size and statistical significance."

There is a strong element of impatience in Leaf's writing and talks – an urge to cut through what he



Critical press. These articles cover many of the issues that Leaf believes are obstacles to progress: fragmentation and poor leadership in the cancer research community, the privatisation of knowledge generated in public institutions and an excessively risk-averse attitude towards potentially life-saving drugs

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calls sclerotic and slow processes. This is partly a result of his background in business journalism.

Leaf cut his journalistic teeth on health, fitness and women’s magazines, while nurturing dreams of being a novelist, before finding a niche at a personal finance title, *Smart Money*. “That’s when I finally thought I’d got a career and was able to write long articles with an element of story telling.” A call from *Fortune* came, and he moved in 2000 to become its Wall Street editor, just before the infamous ‘dotcom’ crash. *Fortune* had long had a reputation for investigative journalism, and Leaf himself wrote a cover story on how corporate thieves were getting away with their crimes. “I wrote about the need to treat white collar criminals with the same severity as any thief.”

When he had a chance to meet Dan Vasella, CEO of Glivec developer Novartis, he wasn’t very interested at first. “But it developed into an extraordinary conversation about the passions of chief executives and our mutual experiences with people who had died of cancer. I ended up writing very favourably about him and his book – *Magic Cancer Bullet*. I thought, here was an amazing targeted medicine that could stop cancer in its tracks.”

That prompted a further article on the evolution of cancer treatment. “I began by looking at what you might call the ‘financial statements’ of our anti-cancer campaign. One thing we financial journalists are trained to do is to look at the numbers.” He soon found official indicators on mortality, incidence, survival, and what was being spent each year on treatment. “The cancer establishment was saying great progress was being made, and yet, here were the data: all the trendlines had been heading the wrong way for decades.” That’s when alarm bells started to go off for Leaf. “It was the kind of spin I’d heard for years in the

corporate world, with chief executives telling you their businesses were in terrific shape just before declaring bankruptcy.”

It’s worth revisiting the mortality position, as recent US figures continue to make headlines such as ‘Cancer on the run’, while the country’s survival figures are said to be well ahead of most of western Europe. When Leaf first looked at the data he soon found that there had been little progress in reducing the number of life years lost through cancer compared with other conditions such as heart disease, from 1980 to 2002. “All the talk of increased survival wasn’t being reflected in the death certificates,” he says, and the cost of treatment was “outrageous” in terms of outcomes.

The latest figures put out by the American Cancer Society indicate a ‘doubling’ of the rate of mortality decline, but Leaf points out that such declines as have taken place are largely down to just one tumour – colorectal cancer, particularly among men. While some other cancers such as lung have gone down, again among men, others have gone up. “But this murkiness allows the American cancer leadership to boast about declining deaths in a number of specific cancers while ignoring the rest. Of course, the reductions in colorectal and lung cancers are mostly attributable to screening and lower smoking rates – not to the billions of dollars we’ve spent on cancer science and drug development.”

Breast cancer – where much effort has gone on targeted therapies – shows very little decline in mortality, adds Leaf. About 40,000 women have been dying each year in the US since 1987.

Leaf has focused on drugs a good deal, led by both the cancer community’s emphasis on the promised land of targeted therapies and his observation of the lack of progress in treating advanced disease.

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An oft-mentioned point he makes is that the vast majority of research grants and drugs are simply not aimed at combating what actually kills people.

“I went to see Harold Varmus – he’s head of Memorial Sloan-Kettering and was previously director of the NCI, and of course is a Nobel Laureate for his work on oncogenes. His line is that it is a miracle we have come so far and that the problems would go away with the targeted paradigm, as demonstrated by Glivec, and by having several therapies working in concert for more complex cancers. I’m not one to call a Nobel Laureate naïve but, given what is known about the diversity and evolution of tumour cell populations, genomic instability, drug resistance and so on, I feel these phenomenally expensive drugs are missing the mark.”

After a nerve-wracking plenary talk at the American Association of Cancer Research annual meeting – in front of several thousand people – Leaf started to receive calls from researchers such as Judah Folkman, the ‘founder’ of angiogenesis, and met other scientists working on the edges of cancer science. “Angiogenesis is a critical idea – that tumour cells send out signals to recruit blood vessels – but post-docs were told to stay out of Folkman’s lab by those who said that he was ‘crazy’. (The same was true of Mina Bissell and her work on the micro-environment surrounding breast cancer, and Howard Temin, who challenged the molecular biologists’ dogma with reverse transcription, turning RNA back to DNA, which has become crucial for understanding the genetic basis of cancer.”)

He has forged a particularly close association with Michael Sporn, at Dartmouth Medical School, an expert in chemoprevention (indeed he is said to have coined the term). It is from Sporn and others in his camp that Leaf has formed his views about the need to intervene much earlier in the cancer process, and they have shed light on where research priorities are going astray, especially the emphasis on trying to tackle genetically unstable, advanced tumours.

Working back, Leaf has now looked at the way researchers are channelled into the cancer orthodoxy



through the many hoops needed to get grants, which he says in the US seem almost designed to iron out innovation. And academic knowledge that is generated is hamstrung by a culture that is slow to share on national and international stages, and which ties findings and tools up with complex contracts and licensing agreements before they can be exchanged among centres. As he wrote in a subsequent *Fortune* article, “Imagine a carpenter having to pay Black & Decker a percentage of every kitchen he builds.” A vivid cancer example he cites is the race to find the BRCA1 and BRCA2 genes implicated in breast cancer where, despite a collaborative effort, a patent for testing now resides with one company founded by the ‘winner’ – though the company was denied a similar patent in Europe.

“People are starting to realise that the IP issue is paralysing academic exchange – we need a universal agreement for knowledge transfer, not each institution having its own.” Publishing is another bugbear – Leaf reckons that a huge amount of information from diverse sources such as symposia is not finding its way into the public domain, let alone into a common database, and he is a firm advocate of open source journals. “One reason many old medicines are only now coming to the clinic for the first time is a failure of our information systems,” he says.

That feeds into another theme he’s majored on – a view that we are being far too cautious in drug testing, erring on the side of safety at all costs. Rather than

Still friends.

Leaf in the bosom of the cancer establishment, at a dinner sponsored by the Friends of Cancer Research, where he was presented with a Leadership Award. Left to right: Ellen Sigal (FOCR co-chair), Lester Crawford (then acting Commissioner of the FDA), Anna Barker (NCI deputy director), Leaf, Marlene Malek (FOCR co-chair), Andrew von Eschenbach (then director of the NCI, now commissioner of the FDA), Janet Woodcock (deputy commissioner of the FDA)

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At home. With wife Alicia Slimmer and daughter Sofia

balancing risks by including the risk of doing nothing, experiences with now-withdrawn drugs such as Vioxx have led to even more caution, he contends, and the protracted processes in the current clinical trials structure are exacerbating delays. Leaf places the blame on regulators (in particular the US Federal Drug Administration) and the pharmaceutical companies, which have essentially created a privatised clinical trials system, where the commercial sponsors call the shots in pushing for positive results above other findings.

“We have been promised early sight of the results, good and bad, on an easily accessible website, which would help identify more quickly what drugs are working and what the toxicities are,” he says. This is not yet a reality. “The other problem we have is testing drugs in combination. We know the answer is likely to lie in chemotherapeutic cocktails. But the regulations – and the unwillingness of companies to add to their financial risk – make it all but impossible to explore the possible synergies of drug combinations until each agent has been approved. Trouble is, once a new drug is approved for sale, there’s often little incentive for the maker to explore novel combina-

tions.” The result, he says, is years and years of unnecessary delay.

As for the most effective agents of change, Leaf is not surprisingly a great fan of advocacy organisations, and is now an active member in the movement through his board position at Susan G Komen, although he is keen not to single it out (it is though probably one of the world’s biggest, having raised over \$1 billion, mostly for breast cancer). He points out that the charities have addressed successfully many grassroots issues such as the quality of mammography, and are now extending their reach to the key infrastructure problems, such as the ‘tissue issue’ (the lack of a biospecimen network), channelling research funds in the right direction, tackling health inequalities, and in Susan G Komen’s case, running international programmes in areas such as the Middle East.

He speaks highly of Kathy Giusti – founder of the Multiple Myeloma Research Foundation – as a role model for knowing how to bring disparate groups together and in rejecting proposals that do not meet a tough research agenda. Mike Milken – the junk bond trader who went to jail – has done much more useful work founding the Prostate Cancer Foundation, which Leaf says has similarly brought this disease into greater focus. He knows most of the top advocates and high-profile survivors, such as Lance Armstrong (of whom he is an enormous fan), from a cancer tour where he has met more than 2,000 players, and he has been honoured with a string of awards.

He has even given a talk at the NCI’s ‘Grand Rounds’ event, calling for a Google-like search engine for biomedical research data, and presented at the President’s Cancer Panel, on research barriers. And despite being a staunch capitalist in most respects he sees healthcare as fundamentally different, and reckons a Democrat as the next US President will pave the way for much needed reforms such as better insurance coverage, and hopefully changes in cancer research. “The American Cancer Society has moved all its marketing budget to push for universal health-

care in the US – it’s one of the most exciting things I’ve seen it do,” he notes.

What is striking about Leaf is that he has engaged the great and the good in cancer without alienating them. As he points out, nearly all have one or more big issues that concern them, “These usually emerge after 40 minutes or so in an interview and they often disagree with others.” Perhaps the best indicator of Leaf’s impact comes from John Mendelsohn, president of MD Anderson, who not only wanted to meet Leaf after his *Fortune* article, but wrote an extensive reply, describing what he had got right and wrong.

On the credit side, Mendelsohn agrees with Leaf’s key points about the funding favouring smaller research projects, the slow speed of clinical trials and the role of intellectual property. “There is no question that IP gets in the way.” But he points out that running research centres is very costly. It was also right to challenge the use of animal models, a lack of translational research, and progress in biomarkers and early detection, but there is significant work in these areas. On the minus side, he considered the effort in understanding the molecular basis of cancer and carrying out basic science to be crucial; that treating chronic disease and not effecting a cure is important (and also done with conditions such as heart disease); and that generally it is unfair to compare the cancer effort with putting a man on the moon.

The advocacy organisations have taken Leaf to heart and agree with most of his views. Nancy Brinker, founder of Susan G Komen, says above all he has given them professional access to the media and a powerful voice, “taking no prisoners” and fostering provocative thinking, “even if some of his ideas are not practical”. Virgil Simons, head of The Prostate Net, says he has ‘mainstreamed’ the issue of healthcare costs, and tried to break down the elitism in the research community and the derivative nature of much research that is funded.

Leaf lives in Brooklyn, New York, with his wife Alicia, who is a filmmaker, and young daughter Sofia. Travel has become the family hobby – and he says

he’d like to live for a spell in Europe, which could make Eurocrats in healthcare a bit nervous.

Journalists hate being the centre of a story – Leaf was reluctant to say anything about his own cancer when writing the first *Fortune* article. Now that he has become well known in the US as an advocate he is surely more comfortable having left the cosy fold of the magazine to be an independent operator, wearing several ‘hats’. Despite his criticisms of the establishment, Leaf says he is an optimist by nature, and is sure that much of what’s broken will be fixed, and there will be a move towards earlier intervention. But he certainly does not believe there will be the kind of breakthroughs by 2015 that luminaries were still predicting in response to his article. There is also a view among some in the upper echelons that the *Fortune* article is now history, despite being written only in 2004. But Leaf maintains there has been little substantial change and he is not letting up.

“My strength, if I have one, is in knowing how little I do know about the science and being willing to ask dumb questions,” he says. “I’m not afraid to ask people about what progress there has been in the cancer battle – and it is surprising how often the experts have difficulty in explaining where we are.” His vision of how science should be done to clarify the position – researchers quickly building on the parcels of knowledge generated by others in an open market – is certainly benefiting from someone who’s knocked on more doors, ruffled more feathers and generated more wake-up calls than probably anyone has in such a short time in cancer.

As Frank Torti, director of the comprehensive cancer centre at Wake Forest University, says: “He asks tough questions. He disarms others with his straight talk and clear thinking. Before Cliff, there was no discussion, no energy and no challenge to the status quo.”

The views of leading players from cancer research, policy making, regulatory bodies, industry and patient advocacy regarding many of the issues raised by Leaf are presented in Grandround, p 22, which reports on a media event, Time for a Reality Check, organised by the European School of Oncology to promote public debate on how to make faster progress against cancer

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