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David Horrobin (1939–2003): a memoir

John Stein

Magdalen College, Oxford, UK

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I have known and admired David ever since he was an undergraduate at Balliol College, Oxford. I was also terrified and slightly jealous of him. He was so effortlessly, self-confidently and obviously brilliant that lesser, self-doubting, mortals such as myself were greatly in awe of him. But he was never arrogant or unpleasant, so one could not dislike him. Everyone agrees that despite his fantastic intelligence, knowledge and originality he was always charming, always smiling and always polite.

In fact I'd heard of David even before he came up to Balliol because my cousin was at Kings College School, Wimbledon and warned me of this genius going to do medicine at Oxford at about the same time as I was. His father, a Methodist minister, had transferred to Wimbledon from Bolton where David had been born and attended Queen Elizabeth's Grammar School. But I didn't really get to know him until 1963 by which time he'd won his congratulatory First and obtained a Prize Fellowship at Magdalen College, Oxford, where Hugh Sinclair's theory that many modern ills, from arterial disease to schizophrenia, are due to deficiency of essential fatty acids was to influence his work greatly in the future.

But at that time he was working with George Gordon in the Oxford University Laboratory of Physiology, recording from nerve cells processing cutaneous sensory signals. I was then working on the control of respiration with John Widdecombe in the same laboratory and we used to discuss all sorts of things in the Common Room. Then we both went on to clinical school, he to St. Mary's, me to St. Thomas's, and our paths didn't really cross again until many years later through a shared interest in neurodevelopmental problems.

What attracted me enormously about David was his unflagging enthusiasm for new ideas and his fearlessly unconventional opinions on almost everything. There were a number of recurrent themes to our conversations: science as the new religion, the inability of Reductionism to solve any worthwhile problems, the shortcomings of pharmaceutical research, particularly in dealing with psychiatric disorders and the failings of peer review. In

this short memoir I would like to describe David's views on these together with the innovative steps that he took to try to improve things.

1. Science the new religion and the poverty of reductionism

"Science is the modern god.... Twentieth-century scientists, like nineteenth-century theologians, make the wildest claims on behalf of their god.... Twentieth-century science charlatans of a myriad varieties offer their panaceas for society and attempt to mislead the people by calling their misbegotten ideas scientific. And bewildered twentieth-century common men have a crude faith in their god which they do not care to have questioned too closely."

I like to think that our conversations in the Oxford Physiology lab. Common room contributed to these ideas which he published in 1969 in a short book entitled 'Science is God'. It was one of the first books published by Medical and Technical Press which David started with his brother and then wife, an Iraqi princess, in order to be able to publish unconventional views. It has gone on to great success.

'Science is God' not only shows David's rousing style but it also encapsulates what we discussed in 1963 about how science is misused. We were mystified why people so easily accepted the idea that if something is 'scientifically proven' it must be correct. Of course actually science can never prove that any statement is true at all; all measurement can do is to disprove what is untrue and determine what is likely to be true. But all so-called scientific facts are provisional and can be overturned by newer discoveries. By 2003 blind faith in science has disappeared however; the average person is much more aware of this and sceptical of 'scientific facts' than was the case in 1963. In fact the pendulum has probably swung too far the other way.

In particular David was worried by the Reductionist tendencies of most scientists. He argued strongly that reducing the study of a complex condition such as

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1	schizophrenia to the level of single genes, single proteins	57
3	or even single cells was never going to explain what goes	
5	wrong with the whole neural system. Investigations of	59
7	the whole system have to continue hand in hand with	
9	cellular level approaches. But it is much harder to get	61
11	funding for systems level studies because it is so much	
13	more difficult to predict their outcome. For example it is	63
15	easy in principle to see how turning the handles of	
17	modern molecular genetic techniques will enable us to	65
19	link schizophrenia with particular chromosomal sites.	
21	Then we can go on to identify the genes at each site that	67
23	are responsible for the linkage; these in turn will point us	
25	to the proteins that are different in schizophrenics.	69
27	This scenario is all very seductive, and its potential	
29	has been wildly hyped, so much so that most drug	71
31	companies have given up conventional kinds of research	
33	and converted to the molecular genetic approach. But	73
35	even if such a simplistic programme did work out, then	
37	what? How will knowing that one protein is slightly	75
39	different in schizophrenics tell us why schizophrenics	
41	display the varied pattern of emotional and cognitive	77
43	symptoms and signs that they do. Moreover what	
45	progress has this expensive exercise contributed towards	79
47	effective treatment of the disease?	
49	David observed that actually the genetic approach has	81
51	yet to yield even one successful treatment. For example	
53	we now know in great detail the mutation that causes	83
55	cystic fibrosis. But this knowledge has not advanced	
	treatment of this condition one iota. David ceaselessly	85
	argued that pharmacogenetics has been greatly oversold.	
	He judged the whole argument to be fatally flawed.	87
	Until there is some method of being able to repair faulty	
	genes in the egg and sperm, a simple genetic approach to	89
	disease will be fruitless. But the prospect of meddling	
	with our germ lines is so fraught with ethical and	91
	practical problems that it is unlikely to occur in our	
	lifetimes. Furthermore rare single gene diseases such as	93
	cystic fibrosis are probably totally inadequate models	
	for the much more complex polygenic and multifactorial	95
	conditions that are practically so much more disabling,	
	such as schizophrenia. David was fond of pointing out	97
	that we share 50% of our 30,000 genes with bananas,	
	and 99% with chimpanzees; yet the interactions of that	99
	different 1% of genes make us incomparably more	
	complex.	101
	David was never tired of pointing out that most drug	
	discoveries are totally serendipitous and could not	103
	possibly have been predicted. Even those that were the	
	result of a logical programme he argued, did not derive	105
	from molecular genetics, but from systems physiologists	
	such as Sir Douglas Black working out how β blockers	107
	might alleviate high blood pressure by blocking the β	
	effects of adrenalin, or gastric ulcers improved by	109
	blocking the histamine receptors that release gastric	
	acid. David used to say that modern biomedical research	111
	has lost all contact with clinical reality. The drug	
	companies are failing the public due to their infatuation	
	with the genetic approach. Year by year there are fewer	
	and fewer new drugs coming on the market despite the	
	astronomical sums the drug companies spend on	
	research, because they've all been seduced by the	
	plausibility of molecular reductionism.	
	2. Peer review	
	Another icon that David attacked right from his	
	undergraduate days was peer review. Its intended	
	function is to target scarce funds to the best research,	
	i.e., that which is most likely to improve human health	
	and to ensure that only such sound research gets	
	published in the Journals. But David argued that by	
	its very nature it succeeds neither in identifying the best	
	research nor in improving human health. He pointed out	
	what he called Universal Rules, namely that real	
	innovations come from totally unexpected directions	
	and that they are almost always vigorously attacked	
	when they first appear. The real paradigm shifts that	
	significantly advance our understanding of how things	
	work are implacably resisted for two main reasons. First	
	most people are naturally lazy and do not want to have	
	to rethink their whole intellectual edifice.	
	However, an even more powerful force against change	
	is the benefit that most people involved in any particular	
	research topic gain from adhering to the current dogma.	
	Their salary and posts in Universities or research	
	laboratories often stem from their contribution to its	
	present pre-eminence. Naturally therefore they have a	
	vested interest in rubbishing any new idea that might	
	undermine it. In David's words "Peer reviewers are	
	always competitors with incentive to find fault." This	
	was the treatment that almost all innovations received.	
	Darwin's blasphemous theory of Natural Selection,	
	Langley's preposterous suggestion of chemical transmis-	
	sion between neurons, and the ridiculous idea that cells	
	may be programmed to die by apoptosis spring to mind.	
	When peer review is used by Grants Committees it	
	becomes even more unreliable. Your ideas are being	
	criticised by your competitors who want to shoot them	
	down, but also have a vested interest in stealing them.	
	This is not just a theoretical concern. We've all seen our	
	ideas that have been refused grant funding then turn up	
	in the papers of your competitor who was probably one	
	of the original reviewers. So the sensible tactic is not to	
	reveal your new ideas, but to only describe what you've	
	already done and hope the reviewers do not notice.	
	Hence the whole system encourages concealment, lying	
	and corruption. "Encourages backstabbing; favours	
	psychopaths" as David said, and sadly we all know	
	that he was right.	
	But this is not even the worst outcome. Any criticism	
	is lethal when resources are limited. So Grants	

1 Committees will almost always choose projects that are
2 the lowest common denominator, not risky, but
3 pedestrian and safe—good, but not the best: ‘A
4 harbinger of mediocrity’ ‘The good is the enemy of the
5 best’ as David said.

6 Indubitably the worst outcome is that the system
7 systematically suppresses innovation. Since scientific
8 progress depends on people having the imagination
9 and courage to try to make paradigm shifts, the
10 paradoxical effect of the way all the Government and
11 Institutional funds that now go into research is
12 managed, is that they slow down scientific progress
13 significantly.

14 David always acted on his convictions. In 1975 he
15 started Medical Hypotheses to take a deliberately
16 different approach to peer review. In David’s words
17 ‘Most contemporary practice tends to discriminate
18 against radical ideas that conflict with current theory
19 and practice. But Medical Hypotheses deliberately
20 courts radical ideas, so long as they are coherent and
21 clearly expressed. Furthermore, traditional peer review
22 can oblige authors to distort their true views to satisfy
23 referees, and so diminish authorial responsibility and
24 accountability. In Medical Hypotheses, the authors’
25 responsibility for the integrity, precision and accuracy of
26 their work is paramount. The editor sees his role just as
27 a ‘chooser’, not a ‘changer’: choosing to publish what
28 are judged to be the best, not the most uncontroversial,
29 papers from those submitted’.

30 In later years David tried to convert the establishment
31 towards a new way of distributing research funds. He
32 recognised that good researchers are a rare breed that
33 ought to be specially supported, rather like artists. They
34 have to be very self-propelled and determined, able to
35 cope with failure and wasted time. For, particularly
36 during the early stages of a project, often nothing seems
37 to work, and things can become very frustrating. There
38 are a million ways of being wrong, but only one way of
39 being right, and most Ph.D. students spend many days
40 in tears of despair. People who take up research have
41 chosen to devote their lives to a very fickle mistress.
42 Their rare personal qualities of intelligence, imagination,
43 determination and their costly acquired skills should be
44 properly nurtured, not rewarded with disdain and
45 perpetual problems of funding because psychopathic
46 competitors have gained control of the system.

47 David saw that the only truly reliable indication of
48 scientific merit and the only indicator that cannot be
49 subverted by the peer review system is the past track
50 record of a scientist because this above all demonstrates
51 their commitment and talent. Therefore, he argued that
52 all available money should be divided equally among
53 such attested productive researchers without further
54 review. This, he calculated, would yield about £100k p.a.
55 per researcher to be used as the researcher saw fit, but

only renewed if the person remained productive in terms
of published work or other performance indicators.

56 This scheme would have several advantages. It would
57 encourage meaningful collaboration (virtual centres)
58 between researchers to pool resources if necessary,
59 avoiding the forced marriages, such as ‘interdisciplinary
60 research centres’ that look so good on paper, and are so
61 beloved by bureaucrats innocent of much research
62 experience.

63 Also under the present system most senior researchers
64 have to spend about 1/3rd of their time writing grant
65 proposals, only 20% of which are successful. What a
66 pointless waste of time! Implementing David’s proposal
67 would release those 20h per week for productive
68 research. And finally perhaps the greatest gain of all of
69 his scheme would be to completely remove researchers’
70 incentive to be corrupt and dishonest.

71 3. Randomised control trials 72

73 In 1979, building on Hugh Sinclair’s ideas about the
74 importance of highly unsaturated essential fatty acids in
75 the body and David’s discoveries about their role in
76 prostaglandin synthesis, he became the first Britisher to
77 start a biotech company, Efamol, to produce and sell
78 evening primrose oil. For a while this was the darling of
79 the Stock Exchange, and David briefly became a very
80 rich man. Evening primrose oil is a rich source of omega
81 6 gamma linolenic acid, and David showed that it was a
82 highly effective treatment for various conditions such as
83 eczema. In the course of his clinical trials to prove the
84 efficacy of these preparations he came to learn a lot
85 about the strengths and weaknesses of what some people
86 claim to be the greatest achievement of the C20th—the
87 randomised control trial (RCT).

88 This was really invented by James Lind in 1753 who
89 used randomly selected sailors to take citrus fruit or
90 other nostrums and showed that only those who took
91 citrus avoided scurvy. Sir Bradford Hill developed the
92 same technique in 1945 to show that streptomycin could
93 cure tuberculosis and the Sir Richards Doll and Peto
94 perfected the randomised control clinical trial to test
95 other drugs. The RCT has now become the absolute
96 gold standard to prove drug efficacy, so much so that
97 almost the only kind of evidence that is accepted as
98 ‘evidence based medicine’ by, for example, the Cochrane
99 Collaboration or the National Institute for Clinical
100 Excellence (NICE) has to be provided by a large RCT.

101 However, the RCT has unfortunately become yet
102 another ‘scientific’ religion supported by its adherents
103 with almost Messianic fervour. For, the RCT is by no
104 means the only way of deciding whether a treatment is
105 useful. It is really only relevant when the effects are
106 relatively small (less than 50% improvement). As David
107 said ‘Barn door effects don’t need RCTs to prove them’.

1 Indeed they are unethical. If patients can see quite
2 obviously that one treatment works and another does
3 not, it is totally unethical to randomise them to the
4 ineffective one simply to satisfy the bureaucratic
5 requirements of NICE.

6 David saw however how useful the requirement for
7 large, expensive RCTs was to the large drug companies
8 for keeping small fry such as Efamol out of the gravy
9 train. In his case the drug companies could also use the
10 same technique to prevent non-pharmaceutical, natural,
11 nutritional products such as essential fatty acids
12 obtaining highly lucrative licences. It is really sad and
13 ironic that his last paper before he died of cancer was
14 'Large trials in rapidly lethal diseases are usually
15 unethical'.

17

19 4. The madness of Adam and Eve

21 In the last part of this memoir I'd like briefly to run
22 through the evolution of David's most important
23 work—the hypothesis that mental disorders are the
24 corollary of the human brain's dependence on fish oils.

25 Apparently it all started when he was a medical
26 student in 1959 and went to Kenya as a flying doctor.
27 Wilfred Le Gros Clark was our anatomy professor at
28 that time and among other things he was an expert on
29 the evolution of the human brain. Wilfred suggested to
30 David that whilst he was in Kenya he should go and see
31 the thousands of hand axes piled up at Olorgesailie and
32 to try to explain why their design remained completely
33 unchanged for over 2 million years.

34 And yet suddenly only about 100,000 years ago they
35 changed utterly. At that time human artefacts and tools
36 advanced dramatically, so that only 50,000 years later
37 the cave paintings at Lascaux and Altamira demonstrate
38 sophistication and innovation unimaginable in the
39 previous 2 million years, but were now equal to modern
40 man's. Something dramatic must have happened to the
41 human brain, and when he was elected to his Prize
42 Fellowship at Magdalen Hugh Sinclair told him what
43 that might have been—incorporation of highly unsatu-
44 rated fatty acids (HUFAs) from fish oils into the brain.
45 At the time David thought this was a wild, typically
46 Sinclair, over the top speculation.

47 But in 1969 at the age of only 30 David took the very
48 unconventional step of going to the new Medical School
49 at Nairobi as Professor of Physiology. There he became
50 interested in the role of essential fatty acids in the
51 production of prostaglandins. Howard Bern, an expert
52 on the role of prolactin in prostaglandin stimulated
53 natriuresis in both fish and human males, came to give a
54 lecture during high summer when no students were
55 around. So David press ganged all the gardeners,
cleaners and kitchen staff to form an audience for the

distinguished visitor, to listen politely to the lecture, but
not to say a word. 57

58 David on the other hand was enthralled. Howard's
59 lecture fertilised the 3 main themes of his life. Why do
60 humans regulate their salt and water balance in the
61 profligate way they do; they would not survive in the dry
62 savanna for more than 48 h without water? What was
63 the connection between schizophrenia and prolactin?
64 And thirdly, the link which connects them all, why are
65 unsaturated fats so important in the human brain? Bern
66 explained how the omega 6 fatty acid, arachidonic acid,
67 is converted under the influence of prolactin into
68 prostaglandin and how this controls the excretion of
69 excess sodium. This is also one of the unexplained side
70 effects of almost all the drugs used for schizophrenia. 71


72 In his wonderful book, 'the Madness of Adam and
73 Eve', published just before his death, he describes how
74 he was able to integrate these three themes into his
75 theory that the big change in the human brain that
76 occurred about 100,000 years ago was the incorporation
77 of HUFAs, derived from fish, into the human body, but
78 particularly into the brain. Fish oils were readily
79 available to emerging homo sapiens due to our
80 semiacquatic existence at the time, as another Oxford
81 professor, Alister Hardy had proposed during David's
82 undergraduate days, of course to much scepticism. This
83 legacy of the ready availability of water during our
84 evolution explains our profligate use of it, and rules out
85 any prolonged period of development on the dry
86 savannah. The coldness of water also explains why
87 humans have so much more subcutaneous fat than great
88 apes, much to the delight of young men contemplating
89 their comely girl friends.

90 It seems that it is the superior reactivity of HUFAs
91 that enabled a huge increase in connectivity in our
92 brains. Neanderthals actually had bigger brains than
93 Homo Sapiens and the size of chimpanzees' brains is
94 only slightly less than ours. It seems that HUFAs are
95 able somehow to promote stronger and more numerous
96 functional interactions between nerve cells. Our great
97 advantage appears to be a 2 orders of magnitude greater
98 number of connections between our neurons than those
99 found in chimpanzees or, probably, Neanderthals. This
100 increase in connectivity enabled us to develop language,
101 symbolic thought, imagination and creativity, in fact all
the things that separate us from chimpanzees.

102 Obviously this idea is difficult to prove. But it has
103 been shown that rats deprived of HUFAs are highly
104 significantly less intelligent than those with free access to
105 them. Likewise recent studies of human babies receiving
106 no HUFAs in their bottled milk have shown that 10
107 years later their IQ is on average 10 points (0.75 of a
108 standard deviation) lower than those receiving HUFA
109 supplements in their bottles. In other words HUFAs are
110 indeed good for the development of the brain as Hugh
111 Sinclair and all our grandmothers first suggested.

Hugh had studied the diet of working people in London's East End and found that this was seriously deficient in essential fatty acids because they had given up eating fish. He knew that HUFAs constitute 20% of the normal weight of the brain. Hence he argued that dietary deficiency of HUFAs would be harmful, particularly to the brain of the developing foetus, hence to the child's cognitive development. Therefore, aged only 23, he set about trying to persuade the wartime government that cod liver oil should be given to all pregnant mothers and young children. Amazingly he was successful, and so most of my generation did benefit from this HUFA supplement. Indeed people now say wistfully that the average UK diet was better in the dark days of the Second World War than it is now. Of course one of Hugh's most sincere and committed disciples was David Horrobin.

But how does all this connect with schizophrenia? David was impressed by two well-documented facts. The first is that schizophrenia is equally common in all societies all over the world, whether economically advanced or primitive. He argued that this means that it must have evolved by significant mutations involving fatty acid metabolism, before these societies began to separate geographically or economically, i.e., about 100,000 years ago, when our big increase in neural connectivity occurred.

David's second insight derived from Sir William Maudsley's great common sense. In honour of this the Royal Bethlehem Hospital (Bedlam) was renamed the Maudsley hospital. Although he was originally quite attracted to the seductive logic of the Eugenists (get rid of the genes causing madness and you'll get rid of madness), Maudsley later became a passionate opponent. As the foremost psychiatrist of his day he came to appreciate that most of the great successful and creative Victorian families harboured relatives who were mentally disturbed. With fantastic vision Maudsley deduced from this that mental problems are often associated with the same genes that endow creativity. In e's words 'great wits are to madness near inclined'. David therefore also concluded that the same genes that produce man's greater creativity and imagination than chimpanzees also lead to man's propensity to overdoing it in the form of the delusions, hallucinations and thought disorders that are seen in schizophrenia and psychotic depression.

Putting these two facts together with the evidence that increased connectivity was conferred on the human

brain by incorporation of fish oils into it leads to the conclusion that the genes for essential fatty acid metabolism that led to the avalanche of creativity that converted the Orgesaile axes into the cave paintings of Altamira were the same that introduced schizophrenia into our world, the madness of Adam and Eve. David Horrobin supported every kind of research that bore on this conclusion including some of my own. He was intrigued by our observation that dyslexia, depression and schizophrenia all seem to run in the same families, and my idea that they could all at bottom derive from impaired development of a particular set of neurones in the brain, magnocells that are important for timing sensory input and motor output.

Whether or not there really is a connection between fatty acid metabolism, the evolution of human language, imagination and creativity, schizophrenia, depression and dyslexia is by no means proven. But David Horrobin played a crucial part in putting this question on the map and supporting most of the original studies researching it, and I am sure his ideas will stand the test of time.

5. David Horrobin

At the end of the Madness of Adam and Eve, David asked his readers to judge whether he was just 'Clever but crazy, a maverick who bored everyone with his off the wall theories'. Others accused him of being nothing more than a controversial snake oil salesman, little realising that snake oil does actually contain a fair amount of useful HUFAs! But it seems that the person who made that remark had a personal grudge and totally undervalued David's remarkable contributions. He was certainly an iconoclast who challenged conventional thinking. But I think he will be remembered as an incisive writer, thinker and brilliant clinical scientist who robustly and courageously exposed the poverty of reductionism, the weaknesses and corruption of peer review, and its generation of serious barriers to innovation, particularly in the pharmaceutical industry. But like Hugh Sinclair, his original, innovative, creative brilliance in suggesting how our evolutionary entwinement with fish oils influenced the development of our brains will only be truly recognised many years from now.