THE DRIVING FORCE

MICHAEL CRAWFORD
& DAVID MARSH

The Driving Force

FOOD, EVOLUTION AND THE FUTURE

Michael Crawford and David Marsh

A Cornelia & Michael Bessie Book

HARPER & ROW, PUBLISHERS, New York
Grand Rapids, Philadelphia, St. Louis, San Francisco
London, Singapore, Sydney, Tokyo, Toronto

This book was originally published in 1989 in Great Britain by William Heinemann Ltd. It is here reprinted by arrangement with William Heinemann Ltd.

FIRST U.S. EDITION

LIBRARY OF CONGRESS CATALOG CARD NUMBER 88-45891

ISBN 0-06-039069-7

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89 90 91 92 93 HC 10 9 8 7 6 5 4 3 2 1

To Sheilagh and Shandra

Acknowledgements

Much contemporary knowledge of biomedical systems comes from experiments on small laboratory rodents and observations on ourselves. Yet there is a wealth of different species, the study of which tells us much about the variation between species and the reason why we are different from rats and guinea-pigs. This was the philosophy which led Lord Zuckermann, as Secretary of the Zoological Society of London, to raise funds and create the Nuffield Institute of Comparative Medicine. It was this philosophy which attracted me to the Institute and so I owe a debt of gratitude to Zuckermann for making the research possible which provided much groundwork for this book. In the same context, I wish to thank the Institute's first Director, Dr Len Goodwin, whose broad vision and knowledge of biology was an essential stimulus and guide.

It was Africa which first shook my understanding of biology and man's place in it. As a chemist with an interest in the gap between medicine and chemistry, I worked and studied at the Royal Postgraduate Medical School to find out what it was all about. It was there that the first step to the comparative approach was insinuated by Sir John McMichael who persuaded my family and myself to set sail for Africa rather than Boston. 'The same people living no more than 100 miles apart have totally different disease patterns – one group has a form of heart disease quite unlike ours – why?'

The year was 1960 and the aim was to establish biochemistry teaching at the University Medical School at Makerere in Kampala, Uganda. Once established, I set about this task with a fervour for convincing my medical students of the importance of molecular biology and a condescending request to the late Dr Rex Dean to give them two weeks of lectures on nutrition. It took about three years to realise that this balance was hopelessly misplaced. But it was only on my return to the UK that the real difference between what we eat today and what man ate through his evolution struck

home with enough force to awaken some dawning of realisation that nutrition mattered.

Makerere contained many people who were revelling in the wealth of opportunity presented by the comparative approach. Professor Shaper's early work made it clear that raised blood cholesterol and blood pressure levels were not a feature of *Homo sapiens* but only of Western peoples. Dennis Burkitt's studies on lymphoma made their contribution to Africa and science and he too, on his return to the UK, suddenly realised the striking difference in the nature of the stools people passed, how that related to their food and to the high incidence of diverticular disease and colon cancer in the UK which was unheard of amongst our African colleagues. Professor Jack Davies, through his contacts at the NIH of the USA, stimulated much of the comparative disease approach by raising the necessary, and for those days copious, funds. Kris Somers and he pioneered much of the descriptive work on endomyocardial fibrosis – the heart disease of the Africans but not the Europeans. Encouraged by Jack, Peter Turner and Brian McKinney, some of us felt bold enough to suggest there might be a nutritional reason.

In parallel to the human research there was also a flourishing group under Dr Richard Laws who was head of the Nuffield Unit for Tropical Animal Ecology. The opportunities for wildlife research were truly remarkable. Dick's studies on elephant populations provided science with a witness of the principles of catastrophic mass-extinction happening in our time. It was a brilliant stroke to incorporate Dr Sylvia Sikes with her interest in studying the pathology associated with this event. In amongst all this, Professor David Allbrook escaped from anatomy teaching to delve into the paleontological past of Africa, and gave me my first lesson on the subject.

My research was greatly assisted by Inge Berg-Hansen who ran the biochemical research laboratory ably supported by Lawrence Mwasi and Keffer Nguli. Neil Casperd from pharmacology was interested in developing the use of drugs via a crossbow, to anaesthetise and translocate wild animals. The common interest in wildlife led to remarkable friendship and collaborative programme on the difference in the nutrient value of wild species compared with the end product of modern farming. In this respect we were

given much help by Mr Silvester Ruhweza of the Uganda Game Department. Phyl Msuya was a constant companion on safari and in the machinations to create the Dar es Salaam Medical School where he later became head of biochemistry and then assistant Dean. Several of our sample analyses were carried out in his department by Aaron Munhambo.

The post at the Nuffield Institute in London offered new analytical technology to apply to the interesting problems which arose out of comparing Africa and Britain. Man is biologically unlike laboratory or domestic species and remains unselected for any particular purpose. He is physiologically still a wild animal but the foods he eats today have only been with him for a short period of a few centuries or less. By then technology could define at least some of the relevant differences and it did: it would simply have been impossible for man throughout his evolution to have eaten such huge amounts of fat (and particularly saturated fat) during the 5 million year period when he relied on wild foods.

My understanding of the biochemical mechanisms was fired by a lecture by Professor Hugh Sinclair in 1966 at a Zoological Society Symposium which explained what fats meant to atherosclerosis and heart disease. It then became clear that animals including ourselves did not only need protein to build our bodies but that they also required fats: the problem was that they had to be the right kinds of fat. I am convinced that if Hugh gave that same lecture today, there is little he would need to change: he was far in advance of the field.

Of course fats were not the only difference between the foods on man's natural background and modern products; but it was clear that they were pretty important to the epidemic of atherosclerosis and heart disease. Mary Gale, who was working with me at the time, made a simple suggestion which actually became quite important.

She commented that everyone was working on atherosclerosis so if we were interested in fats, why not work on the brain which is made more of fat than anything else! The establishment of the day did not like the idea that our cows might be killing us (as the *New Scientist* put it). The antagonism from the establishment helped to cement the change in direction for which they are now to be thanked. The brain after all was the most signficant feature that made *Homo sapiens* different from chimps and buffaloes and very little was known about its chemistry and even less about its links

with nutrition. It was tacitly assumed that the brain could make all the fats it needed but that idea was based on poor analytical chemistry which failed to reveal the presence of long-chain essential fatty acids.

In the investigation that followed, there were many who contributed far more than I; Andrew Sinclair joined me from Canada and soon found the level at which you could feed enough essential fatty acids to let laboratory rats become pregnant but not enough to satisfy the requirements for proper brain development. Whilst everyone else was working on rats, which can perform metabolic miracles with nutrients, John Rivers contributed substantially by showing just how difficult it was for the cat to make the long-chain essential fats which it needed for its brain: the cat relied on other animals to do the job for it. John was also a most stimulating colleague: he could always find something new to say. It was for this reason that David Marsh and I were glad that he read and commented on this text.

In the meantime, comparisons of different species was showing that brain size seemed to be related to amounts of these special essential fatty acids that the lifestyle of a species could achieve. Putting the experimental and the comparative data together spelt out a long-range link between nutrition and the brain. Dr Ahmed Hassam then filled in many of the details and Professor Pierre Budowski descended on us from Israel to forge a new dimension in our understanding of the need for both families of essential fatty acids for the brain. In the meantime Wendy Doyle tested the relevance of the data to pregnant mothers. Whilst Patrick Drury built all the necessary computer software, Martin Leighfield, Ann Lennon and many others conducted the difficult analyatical procedures. The medical aspects could not have been envisaged without the active participation of Drs Bernard Laurence, Kate Costeloe and Alison Leaf and many others.

The applied aspect of our studies was greatly enhanced both scientifically and from being given a sense of purpose through the support from and close co-operation with Action Research into Multiple Sclerosis both from the London and Northern Ireland groups. John Simkins quickly took on board the significance of nutrients to the brain in relation to MS, and through their support, and the encouragement of Ann Walker's group in Belfast, much new ground has been covered and questions raised, the answers

to which we believe can lead to beneficial management of the disease.

Many others in the small band of international workers also made special contributions to the knowledge used in this book. There are too many to mention but Claudio Galli from Milan developed, at the earliest stage, a similar interest and helped present the case for essential fatty acids at an expert meeting called conjointly by FAO and WHO in 1977. Ralph Holman, Bob Ackman, Jim Willis, Bill Lands, Serge Renaud, Michel Lagarde, Peter Ramwell, Howard Sprecher and a few more of us banded together to set up two international congresses for the field, the first as a Golden Jubilee celebration for the discovery of essential fatty acids and prostaglandins and the second to mark the Nobel Prize awarded to Bergstrom, Sammuelson and Vane. The publications of the proceedings were landmarks as well as being collections of vital, readily accessible information on the subject.

Sir Alister Hardy's theory of the aquatic ape was brought to my attention by Stephen Cunnane who had himself written on the subject. Previously, Andrew Sinclair and I had dreamt up the idea that the difference between the carnivore and the herbivore was based on the contrasting availability of the fatty acids specifically required by the brain. This idea was presented at a meeting on the brain organised jointly by the CIBA and the Nestlé Foundations in 1972. The biochemistry regarding the big human brain did not fit with the savannahs which everyone saw as the site of origin for *Homo sapiens*. How could one challenge this view which was held with such strength, simply on some biochemical calculations which suggested a role for seafoods? When Stephen pointed out that the physiology fitted with a marine origin, then 'Homo aquaticus' was born. There will doubtless be many who will argue against the idea of 'Homo aquaticus', just as they dismissed Hardy's original hypothesis: however, the agreement between the physiology and the biochemistry in support of an aquatic origin presents a formidable case. I have to thank Dr Stewart Barlow as Director of the International Fish Meal Manufacturer's Association for offering the opportunity to present the biochemical case at their Munich AGM in 1985. He had lost a key speaker so asked me to fill the gap and tell them how important fish was in the diet! More scientific detail was added at the Membrane meeting organised by Dr Alexander Leaf and his colleagues in Crans sur Sierre two years later and led to Chapter 9, the request by the Swedish Society of Medicine and the Swedish Nutrition Foundation to review the evidence on diet, heart disease and cancer provided the basis for Chapters 12 and 13. David and I are particularly grateful to Maurice Temple-Smith for his patient and valuable assistance in editing the manuscript.

Lastly, I need to mention Bill Pirie who also read the text. This does not mean to say he agrees with anything we say. The comment I want to make is that much of my own insight owes its origins to listening to him and reading what he had to say about biology. It was he who, for example, pointed out to me that the squirrel had the same relative brain size as *Homo sapiens*, a fact which assumes some importance in the discussion on the origin of the 'big brain'.

Science is moving too fast for any single person to keep pace with the rate at which knowledge is accessed. For this reason, the arguments presented in this book are offered from the limited domain of biochemistry in which we have some expertise. The animal examples are again confined to but a narrow aspect of the products of evolution for the same reason. The hope is that their anaylsis may assist in building a wider view of the events which shaped species and ultimately led to man. It is with humility that David and I have set down the words to present a new view of evolution. It is basically a chemical view but we hope is complementary to conventional theory.

M. A. Crawford, London, 1989

Thanks to all the doctors and scientists who patiently explained their theories during my research. To all in the Library at the Institute of Zoology, and in the department of Biochemistry and Nutrition at the Nuffield Institute of Comparative Medicine for their help over seven years; and most particularly to my wife Chandra for years of patience and understanding, for reading, rereading, and reordering innumerable versions of the text, and especially for achieving the final edit of the history of the evolution argument. Without her, the book in its present form would not have been achieved.

D. E. L. Marsh, London, 1989

The Driving Force

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Introduction: the order of life

The multitude of living forms with which we share our rich and beautiful world strikes us with its amazing and incredible diversity. From the moss on the rock to the great oak tree growing above it, from the sea-squirt to the whale, from the single-cell bacterium to man himself, the span of life is immense. How could it ever come about that the barren minerals of any empty planet, themselves typified by the monotony of the moon, somehow shaped themselves into living beings, which changed and multiplied to produce the great spectrum of life that we see all around us?

Men have made many attempts to solve this mystery of life. From the earliest times, philosophies and religions have proposed their answers. But in the last century a single theory has come to be generally held, the theory of an unfolding evolution. In particular, scientists and public alike now accept what they take Charles Darwin to have said about 'random variation' and 'the survival of the fittest'. The force that drove forward the progress of life was simply small, random changes in genetics leading to the development of forms that were fitter or better equipped to survive in the prevailing conditions. Existing life forms would from time to time happen to give birth to progeny which differed in some way from their parents. These mutants would generally be ill-fitted to their environment and would die, but occasionally some would be better fitted for it, and these would survive. In time, as the struggle for existence went on, they would displace the older and less well adapted form. So plants and animals slowly changed until, after a long accumulation of mutations, each one perhaps insignificant in itself, a new species would emerge. The idea of natural selection was thus conceived.

This theory has survived many criticisms and undoubtedly it is one of the greatest intellectual leaps of mankind. It has taken on board the science of genetics and, in recent years, the understanding of cells and their reproductive mechanisms. Out of these various theories it has formed a synthesis that seems impregnable. Yet it has not been without critics, and criticism has not come only from people affronted because the doctrine of evolution seems to contradict the sacred writings.

The thesis however contains one important oversight. Darwin considers how species changed little by little to become what they are today. He does not discuss how it all happened in the first place.

There is also a separate problem which is not of Darwin's making. He rewrote his thesis several times and attempted to find the solution to a problem which worried him. How, exactly, did species interact with their environment? By asking that question he recognised that natural selection was not the only operational force in evolution.

Darwin said there were two factors of paramount importance in evolution: natural selection, and what he termed 'conditions of existence' – we would say chemistry, or the environment. He argued that as natural selection was dependent on 'conditions', then conditions were the most important of the two controlling factors.

So original Darwinism perceived the environment to be a major directive force, although a precise mechanism of how environment interrelated with natural selection was not clear. It was this problem that Darwin spent the rest of his life trying to work out.

People who came after Darwin rejected this question and neo-Darwinism now sees selection as the only mechanism for evolutionary change. Through briefly reviewing the history of evolution theory, it can be seen, firstly, how this came about, and secondly, how a contemporary understanding of biochemistry can throw light on the sort of mechanism for which Darwin and others after him were looking.

There are several recurring objections to the narrower 'post-Darwin' view of evolution. One objection can be put in the form of a simple question: 'Has there been enough time?'

Many scientists have questioned the 'collection of small, random changes' as a mechanism for the origin of life, let alone new species. Indeed, Albert Szent-Györgyi, the scientist and Nobel prize winner, has presented the case that the probability of life emerging by chance is *zero* (Szent-Györgyi, 1977). The Cambridge astronomer, Sir Fred Hoyle, like Szent-Györgyi, was so convinced by the mathematical implausibility that he abandoned the idea of evolution taking place on our own planet and proclaimed that it must have arrived from outer space. In this book, we shall simply suggest that the principles of chemistry and nutrition remove the element of chance.

It is instructive to look at a well-known analogy that was used to justify the chance process suggested by Darwin. The analogy is commonly attributed to T. H. Huxley, a leading figure in British science, who is supposed to have invited his readers to imagine a group of monkeys, each at his own typewriter, hammering away at the keys in a totally random way. In time, it is said, they would type out the complete works of Shakespeare. Mathematically this is perfectly true. In time they would; but the question is, how much time? To test this out, we wrote a computer programme to calculate how long it would take for one of Huxley's monkeys to type out just the first line of a single Shakespeare sonnet. The programme ran, and the computer informed us that the answer was too large a number for it to print. At this stage we realised that you do not need a computer, simply a table of logarithms. By converting the problem to logarithms we were able to get a result, and it was quite startling. If a monkey went on untiringly hitting three or four keys every second – say two hundred a minute – the job would take just under thirty billion years. If he had started typing at the moment when the universe began, he would still be nowhere near halfway to producing that first line of verse.

What we forgot was that a typewriter has at least 45 keys not 26! (And that does not include upper and lower case.) When we told N. W. Pirie about our problems with the computer he remarked that when he was at school, a master tried to use the same argument about monkeys. He immediately pointed out that with 45 keys and (say) 30 letters in a line, guessing that the log of 45 was 1.7, you had a 50 figure number for the possible permutations. A computer is not needed.

This, of course, no more proves Darwin wrong than Huxley's analogy could have proved him right. What it does show is that arguments about what will occur by random change are valueless if we do not consider the actual logistics compatible with the mechanism. Although science has yet to describe the full range of numbers and the chemical mechanisms involved in evolution, it is astonishing that so many have swallowed this monkey business!

Hoyle is by no means the only critic to believe that, for a simple model of the evolution of life and natural selection, the numbers do not fit. Professor C. H. Waddington, a geneticist who did much experimental work with animals, has compared the theory of evolution through chance to a builder 'throwing bricks together in heaps' in the hope that they would 'arrange themselves into a habitable house'.

These simple demonstrations give some idea of the sizeable mathematical constraints which convinced Szent-Györgyi, Hoyle and Waddington, among others, that evolution could not have happened by chance alone.

So how could it have worked? Chemical molecules are themselves built to specifications which depend on the nature of the chemicals reacting together. This property of chemicals is not lost simply because the chemical is part of a living system. Hence the chemicals which interacted to produce what we now call the genetic code and the further interaction with proteins, RNA and other molecules, had to be arranged in response to the options set by the laws of chemistry and physics. This targeting by the laws governing how one chemical reacts with another simply takes the guesswork out of the game.

However, those with faith in the lottery have fought back. A computer programme, if given rules, can readily assemble meaningful phrases out a jumble. Richard Dawkins uses this technique in his book *The Blind Watchmaker* (Dawkins, 1986). To solve the Huxley paradox he analyses the data on the basis of cumulative selection whereby the first selection restricts the possibilities for subsequent selections; in so doing the number of options is dramatically reduced to a point where it is all possible by chance. However, this technique does not solve the paradox. What Hoyle and Szent-Györgyi are worried about in the first place is not selection but the origin of life itself; selection comes at a much later stage. The difference between one species and the next is tiny in comparison with the difference between the presence and absence of life. If, however, the beginning of life was the dedicated work of chemistry, then we need not consider chance.

The rules of chemistry are not quite blind and were made long before life evolved. It is not a question of a blind maker but one with its eyes wide open to the laws of chemistry. The important distinction between blindness and rules is that rules allow predictions to be made about associations and directions. This is the basis of the scientific method and when scientists get it right, the predictions are proved correct. Rules enable us to predict what happens when A meets B. Hence chance can be replaced by an inevitable chemistry and the Huxley numbers are brought down to a manageable size.

The numbers involved in the creation of life by random events are difficult to comprehend and it is also difficult to ascribe to chance the simpler question of the evolution of the sophisticated hierarchy of living things. This difficulty is illustrated by a consideration of what needs to happen for what appears to be a single new modification to succeed.

Let us consider the long neck of the giraffe which has been used often in the debate on natural selection. Those animals with slightly longer necks than their friends survived because they could reach higher into the trees and so gain the advantage of reaching foods that others could not.

If, say, some forerunner of the giraffe was born with a slightly longer neck than its parent, the greater length would be valueless if the animal did not also modify its heart to pump enough blood at increasing pressure to meet the greater demand, and its vascular system to take the strain. Its nervous system too, must change. Unless it develops some pressure-regulating valves in the blood vessels leading to the brain, then every time it lifts its head from drinking water, it will simply black out as the blood drains from the brain. Its pattern of behaviour must also change if it is to seek its food from the tops of trees. If the food that is now brought within its reach is different from that which its shorter-necked parents browsed on (and we shall see that it is), then its stomach and digestive system will also have to be modified. So it is not just the time needed to develop the gene for a long neck; the time taken for all these other essential changes to coincide also needs to be taken into account.

Unless there is some mechanism linking these changes, the chances against them all happening simultaneously are enormous. The changes taking place are not just cumulative but are also co-ordinated. Indeed, throughout the different lines of evolution, they are so co-ordinated that it is far from likely that chance alone could have produced the great variety of living forms that have come into