Chapter 12
Cholesterol and Cardio-Vascular Disease: Degenerating Research Programmes in Current Medical Science

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Abstract This paper argues that, when examined from a Lakatosian perspective, the (mini-) research programmes that have been built to defend two important theories in modern medicine show all the marks of consistent empirical degeneration. Yet those two theories remain enormously influential—underpinning, as they continue to do, advice and treatment given to millions of people worldwide. As Lakatos and others have shown, theories in successful sciences, such as physics and chemistry, whose associated research programmes have degenerated have invariably been rejected. This is an area, then, in which Lakatosian ideas might have enormous impact—if the verdict of degeneration is correct and if it were accepted by the medical community, it could lead to change of medical treatment for millions of people. The final part of the paper looks at reasons why recommended treatment has so far *not* changed despite the apparent degeneration of the supporting research programmes. It therefore takes us into another area of Lakatosian scholarship—his much-discussed distinction between 'internal' and 'external history of science'.

Keywords Ad hoc · Independent testability · Degenerating research programmes · Cholesterol · Cardio-vascular disease · Statins · Internal and external history

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As noted in the entry on his work in *The Stanford Encyclopedia of Philosophy,* Imre Lakatos was "very much more than a philosopher's philosopher".[1] In particular, researchers in a variety of fields—Biology, Psychology, International Relations and Management Science amongst them—have found it enlightening to conceptualise pieces of theorising in their subjects as research programmes and to assess them for progress or degeneration in Lakatosian terms.

This paper concerns a *potential* impact of Lakatos's ideas outside of philosophy—in fact in contemporary medicine. I will show that a whole series of steps in two "mini-programmes" built to defend influential medical claims constitute clear-cut cases of Lakatosian degeneration. While I cannot here survey all the evidence for all the very many saving hypotheses potentially involved in these two mini-programmes, I do hold that I make a *prima facie* case for the overall degeneration of those mini-programmes.

Assuming that a full analysis of all the evidence would bear out this judgment, then one would have expected both of the hypotheses involved to have been firmly rejected. But the reality is very different. The second hypothesis in particular continues to be very widely accepted in medicine and to form the basis for advice to, and treatment of, millions of people worldwide. As for the first, the consensus that it attracted for decades has recently shown some signs of breaking up, but it continues to have a firm hold on public opinion and certainly remained accepted as true and as the basis for dietary and medical advice long after the research programme built to defend it had shown clear signs of degeneration.

I hope that by characterising the situation in explicitly Lakatosian terms and hence relating it to cases in "harder" sciences such as physics, where such degeneration has historically always led to the rejection of the theories/research programmes at issue, that this will strengthen the hand, and hence the influence, of those few within medicine who have been and remain sceptical about the hypotheses concerned.[2] And hence that it will have an impact, both on the science and its application (in terms of approved advice and treatment).

In the final section of the paper, I will address the conflict between the judgements arguably supplied by Lakatos's methodology and what has actually happened—and is actually happening—in medicine. This will point us in the direction of "group think", vested interests and vast amounts of money via Lakatos's famous (some might hold, infamous) distinction between "internal" and "external history" of science.

[1] My academic career would never even have started without the inspiration, guidance and support of Imre Lakatos; and so, it was a special pleasure and honour for me to present a plenary address at the "Lakatos @100" Centenary conference held at LSE in November 2022. This paper is a revised version of that presentation—some revisions having been made in response to helpful criticisms from a referee.

[2] These include Dr. Malcolm Kendrick, to whose 2007 and 2018 books this paper is greatly indebted.

12.1 Methodological Preliminaries: Adhocness, Independent Testability and Degeneration

I will turn to the medical examples very shortly, but first some preliminary clarificatory remarks about degeneration and its relationship to adhocness. Many—Paul Feyerabend amongst them[3]—interpret Lakatos as identifying the two notions: as in effect claiming that

- A shift in theory constitutes degeneration just in case the new theory is an ad hoc response to some experimental difficulty or anomaly for its predecessor theory.

If it were committed to that identification then of course Lakatos's position would be refuted (just as Feyerabend claimed) by instances of theories that, while definitely ad hoc, were also clearly scientifically valuable. But endorsing that identification would be a mistake—not one that Lakatos in fact made. On the contrary, had he still been alive to hear it, Imre would have fully agreed with a talk given at the Popper Seminar at LSE in the 1970s a few years after his death. The talk was by the experimental physicist and historian of science, Allan Franklin, and was entitled "Ad hoc is not a four-letter word". Franklin's message was not, of course, the trivial literal one, but instead a much more systematic version of Feyerabend's thesis that there are many theories in science that were produced only as ad hoc responses to some difficulty for a predecessor theory but should clearly count as good progressive science.[4]

Some theories are *both* ad hoc *and also* clearly scientifically unacceptable. My favourite example was provided by Philip Henry Gosse. In his book *Omphalos: an attempt to untie the geological knot* (1857), Gosse defended what later came to be called Young Earth Creationism (the view that the Universe was created in 4004 BC or thereabouts) against the evidence that many parts of the Earth's furniture seem to be much more than 6000 or so years' old by shifting to the theory that, just as God had created Adam with a navel despite this being an unnecessary, even misleading embellishment in Adam's case ("Omphalos" is Greek for "navel"), so God had created the universe in 4004 BC or thereabouts with many aspects of the Creation looking already very old. (Gosse never, it seems, made it clear why he believed he knew that Adam had a navel—I could find no mention of this aspect of Adam's anatomy in the *Book of Genesis*.) Gosse's hypothesis is both patently ad hoc and patently unscientific, but it is unscientific, not because it is ad hoc, but rather

[3] See for example Feyerabend (1975).

[4] Several different notions of adhocness can be found in the subsequent literature—many of them with automatic negative ("four-letter word") overtones. It is important to emphasise. Therefore, that this Lakatos-Feyerabend-Franklin debate makes sense only if 'ad hoc' is understood, as it is throughout the current paper, strictly in the literal sense of 'being introduced to deal with some particular difficulty as opposed to planned in advance'. (See for example *The Cambridge Dictionary.*) In the case of theories, this means introduced purely to deal with some difficulty in the form of an experimental anomaly for an earlier accepted theory.

because it is totally untestable independently of the phenomena it was constructed to explain. (Indeed, it is constructed precisely to guarantee that there is no independent testability.)

Consider, by contrast, the theorizing of Adams and of Leverrier that resulted in the discovery of the planet Neptune. Herschel had earlier discovered the planet Uranus simply through careful observation of the night sky. When Uranus's orbit was calculated using Newton's theory, the calculations were in significant disagreement with the observational results concerning that orbit. Adams and, independently, Leverrier produced a clearly ad hoc defence of Newton's theory. They took it that that theory had to be correct in view of all the other evidence in its favour. But in effect made the Duhemian point that no testable prediction about Uranus's orbit follows deductively from Newton's theory taken in isolation. Amongst other assumptions, some hypothesis about the total gravitational force acting on Uranus is clearly needed: there might, Adams and Leverrier each suggested, be a still further planet which was so far unknown and hence whose gravitational influence had not yet then been taken into account. And, working back from the assumption that Newton's theory was correct, they calculated what that extra gravitational influence had to be in order to yield correct predictions about the orbit of Uranus. Those calculations amounted to the prediction of the existence of a hitherto undiscovered planet—subsequently observed and named Neptune. Clearly, the Adams-Leverrier hypothesis was ad hoc: the postulation of the extra planet was motivated solely by the desire to defend Newtonian physics against the initially anomalous data concerning Uranus. But it led to a verifiable prediction, independent of the now correct "predictions" about Uranus, and that independently testable prediction was confirmed (Neptune really exists and can be observed). No wonder this is so often cited as one of the great success stories in the history of science: a great success for ad hocness!

So, the key question so far as the progressiveness of a theory-shift is concerned is *not* whether or not that shift was an ad hoc response to experimental difficulties encountered by the earlier theory (the theory shifted from). Instead, the key issue is *independent testability*.

- A research programme is **progressive** if and only if its successive theories are always independently testable in principle, sometimes independently testable in practice *and* confirmed in (at least some of) those independent tests.
- A research programme is, on the contrary, **degenerative** if and only if each new theory explains only the evidence that was anomalous for its predecessor and has no *independent* success: meaning *either* that the new theory is not independently testable at all *or* that it does make independently testable predictions but those predictions are themselves falsified—requiring a further shift that in turn has no independent predictive success *etc*.

Here 'independent' always means: different from any data that were anomalous for the predecessor theory and were worked into the later theory. The modified system of classical physics created by Adams and Leverrier was bound to entail the correct orbit of Uranus—it was specifically engineered to do so. The surprise and therefore

the confirmation comes from its correct prediction of the hitherto unknown planet Neptune.

I now turn to the medical examples. As we will see, all the theory-shifts involved in these examples of "mini-research programmes" that I shall cite are patently ad hoc; but, as we have just noted, that in itself is not necessarily a scientific defect. The key question is always whether or not the theories shifted to are independently testable and independently confirmed.

12.2 Cholesterol and Coronary Vascular Disease

A number of relationships between diet (specifically foods high in cholesterol and/or saturated (animal) fats), "blood cholesterol level" and Cardiovascular Disease (CVD) have been alleged to hold over the years since the "Diet-Heart hypothesis" was first publicised by the nutritionist Ancel Keys in the 1950s. I will concentrate on two. They are.

- Theory 1: A diet high in saturated fats causes (i.e., is a positive risk factor for) CVD—via its effect on "blood cholesterol".[5]
- Theory 2: A "high" blood cholesterol level—independently of how it got to be high, whether through dietary or other reasons—causes (i.e., is a positive risk factor for) CVD.

The two main forms of CVD are heart attacks (myocardial infarctions) and ischaemic strokes.

The story of the overall "Diet-Heart Hypothesis" is full of twists and turns, involving several changes in the meanings of key terms. In order to avoid over-complicating matters, I restrict myself to one preliminary clarification. Since cholesterol is not soluble in blood, you, strictly speaking, cannot have a blood cholesterol level whether high or low. Instead, cholesterol is carried round in the blood as a component, along with some fatty acids, of a lipoprotein. These lipoproteins come in various forms and sizes and, when not ingested from food, are manufactured in the gut or (mainly) in the liver—they range from VLDLs (very low density lipoproteins), also sometimes categorized as triglycerides, to IDLs (intermediate density lipoproteins, formed from VLDLs when they lose triglycerides to fat cells), these in turn may shrink to form LDL (low density

[5] Defenders of the 'Diet-Heart Hypothesis', like Keys, initially stressed the role, not of saturated fats but of dietary cholesterol (from, for example, egg yolks and avocados) in (allegedly) causing high blood cholesterol and hence (allegedly) CVD. However, even its most fervent initial advocates, including Keys himself, soon found intolerable the degeneration involved in defending the dietary cholesterol part of the hypothesis. So nowadays (almost) no one mentions dietary cholesterol and the emphasis is (almost) exclusively on saturated (animal) fats. Despite its interest, I omit the part of the evidential story about the demise of the dietary cholesterol hypothesis in the interests of brevity.

lipoproteins) and finally the smallest lipoprotein is HDL (high density lipoproteins). It was LDL that was eventually identified as the alleged bad guy in terms of increased risk of CVD. A later twist—one that we will eventually consider in some detail—saw the emergence of the theory that, while a high level of LDL is a cause of CVD, a high level of HDL is, on the contrary, *protective against* CVD. I shall from hereonin follow the now usual (though distinctly odd) practice of talking about 'LDL-cholesterol' (so called "bad cholesterol") as opposed to 'HDL-cholesterol' ("good cholesterol"). Hence the two claims whose evidential status we will investigate read:

Theory 1: A diet high in saturated fats causes CVD, via its effect on LDL-cholesterol.

Theory 2: A high LDL-cholesterol level in the blood (independently of how it got to be high, whether through dietary or other reasons) causes CVD.

Both of these claims should, I believe, be rejected as false on the basis of all the evidence. As noted earlier, I shall not pretend to show this fully here. A full demonstration would in any case involve a number of elements—especially the logic of the confirmation of hypotheses that are "causal" but non-deterministic—to which Lakatos, in common with all the other philosophers of science of his era, gave scant attention at best. However, one central plank of the case for a negative evidential judgment about theories 1 and 2 is also a central notion in Lakatos's methodology of scientific research programmes: namely degeneration. I shall show that the development and defence of both theories have been beset by several instances of classic Lakatosian degeneration.

12.2.1 A Problem for Theory 1: The "French Paradox"

One objection to theory 1 (that a diet high in saturated fats causes CVD) was raised long ago, has been much discussed and is generally referred to as "The French Paradox". Compared to people from the UK, the French—on average of course—consume considerably more saturated fat as a proportion of their total diet (they also smoke more and exercise less), and have a (fractionally) higher average LDL-cholesterol level; but, despite the higher fat consumption and the (slightly) higher LDL level, the French rate of CVD and of death from CVD is not just lower than the UK rate, it is around *one quarter* of the UK rate. So, higher saturated fat consumption, yet strikingly lower rate of CVD and of CVD deaths. This looks like a problem for theory 1. In fact, the French have the highest rate of saturated fat consumption and the lowest rate of CVD in Europe. (Incidentally, the second highest in the fat consumption stakes is Switzerland which also has the highest average LDL level in Europe but the second lowest CVD rate after France. The country with the lowest rate of saturated fats as a proportion of overall diet is Russia, which happens to have the highest rate of CVD and CVD deaths. So quite a lot of initial "paradoxicality" surrounds Theory 1!)

This fact about the French compared to the UK diet has long been known and so, unsurprisingly (and of course quite justifiably), there have been responses to it from those who continue to defend Theory 1. One response was that the recorded lower rate of CVD in France was not real, but rather a reflection of some difference between the criteria applied in France for counting a death as a death from CVD, compared to the criteria applied in the UK and elsewhere. (What counts as 'cause of death' on a death certificate is by no means always a straightforward matter.)

Well, this hypothesis is certainly ad hoc, but, as noted, ad hoc is not a four-letter word; and the real question is whether or not the hypothesis is testable. And it clearly *is* testable—French practices of classifying deaths as from CVD or otherwise can be checked. The WHO (World Health Organisation) recognised this and sent a team to make exactly that audit: the result was that the French doctors were classifying CVD deaths in precisely the same way as those from the UK. Ad hoc response, testable but no confirmation equals one form of degenerative step.

A second response to the French Paradox was the suggestion that the French have not yet had a relatively high saturated fat diet for long enough for the (alleged) effects to be felt in terms of increased CVD and CV mortality.

> "We propose that the difference is due to the time lag between increases in consumption of animal fat and serum cholesterol concentrations and the resulting [sic] increase in mortality from heart disease – similar to the recognised time lag between smoking and lung cancer." (Law & Wald, 1999)

This "time lag" theory clearly requires the identification, and dating, of some major change in the French diet toward greater consumption of animal products and that is by no means straightforward. But assuming this problem to have been solved, the theory is testable provided that some sort of time period is specified at which changes in CVD rates will start to become visible. (If defenders of this hypothesis are allowed to wait forever for the change then that hypothesis is almost Gosseian in its untestability. Popper's favourite category of unfalsifiable hypotheses was, remember, the "purely existential" hypothesis.) Suffice it to say that this saving hypothesis was first advertised in 1998 (published 1999) since when the French diet has been essentially unchanged and its CVD rates have gone downwards not upwards (see European Heart Network and European Society of Cardiology, 2012).

The most popular response to the "French Paradox", however, is a different one and in fact amounts to a response-schema: a diet high in saturated fats does indeed make CVD more likely, even among the French, *ceteris paribus*, but some other factor X in the French diet (or perhaps in their way of life more generally) intervenes to make other things in fact *un*equal via X's having a contrary and positive effect—one that more than compensates for the negative effect of the saturated fats. Left with X unspecified, this is again untestable, but there have in fact been many attempted specifications on offer. And, so long as some confounding factor is specified, there is nothing unscientific about responding to difficulties for an initial hypothesis in this way. There is, after all, no reason why the impact of diet, or indeed any lifestyle factor, on some disease should not be simply part of the picture—multiple factors may be involved and may be" mixed": some conducing toward the disease

and others protective against the disease). Indeed, many diseases are known to be multifactorial in this way. The issue, as always, is testability and success in tests: if the "French Paradox" is to be resolved scientifically in this way, then the extra, allegedly protective factor has to be specified, tested and the evidence provided by the test should support the claim that the specified factor is indeed protective against CVD.

As indicated, there has been no shortage of contenders for dietary factors (allegedly) found more often in the French than in the UK population and (allegedly) protective against CVD: extra garlic consumption, extra consumption of red wine, and more lightly cooked vegetables amongst them. All of these have been tested—by the obvious method of a controlled trial in which some participants are given a diet high in, say, garlic and the others form a control group with no garlic in their diet—and those tests have generally been failures. Of course, you would have to run the RCT for many years in order to compare rates of CVD and CVD deaths in the two groups, so these investigators use a proxy outcome in the form of lowering of blood cholesterol, (that is, in effect, they assume that theory 2 is correct). Serious studies find no difference even in this proxy marker (see Kendrick, 2007, Chap. 6.) There are some studies that claim to find a small effect of "garlic supplements" in reducing moderately raised cholesterol levels. (See, for example, Ried, 2016.) But these studies are invariably sponsored by the "natural foods" lobby.[6] So far as I can tell, there is no evidence at all that garlic consumption, in any form, affects the variables of real interest: cardiovascular mortality and all-cause mortality.

As for red wine, some studies have endorsed a small negative correlation between moderate alcohol consumption and CVD, but even if it is true that there are more French than UK moderate alcohol drinkers, the effect is much too small to account for the observed France/UK difference in CVD rates. Other attempts to specify the factor X have been even less successful empirically. So again ad hoc but testable theories have been proposed to defend theory 1, but garnered no independent confirmation.

12.2.2 Other Problems for Theory 1

One trial performed as part of the Framingham project (which has been running since 1948—see www.framinghamheartstudy.org) found that eating a high-fat diet was associated with a *decreased* rate of (ischaemic) stroke. Given that ischaemic

[6] The list of organisations involved in sponsoring the Ried (2016) research, just cited, is impressively long and includes the American Botanical Council; the American Herbal Products Association; Bionam; Eco-Nutraceuticos; Healthy U 2000 Ltd.; Nature's Farm Pte. Ltd.; Nature Valley W.L.L.; Organic Health Ltd.; Purity Life Health Products L.P.;Vitae Natural Nutrition; Wakunaga Pharmaceutical Co., Ltd.; and Wakunaga of America Co., Ltd. Wakunaga of America, Co., Ltd., for example, describes itself as "a privately held, family-owned health and wellness company dedicated to offering high-quality dietary supplements."

stroke is one important form of CVD, this again looks like a direct problem for our theory 1. As always, ad hoc responses are, however, available. For example: ah! but strokes primarily affect the elderly; no doubt their fatty diet is causing many to die of heart disease before a stroke gets the chance to despatch them.

An ad hoc hypothesis, but again clearly testable and those involved in the Framingham sub-study just mentioned had in fact already tested *and refuted* it:

> "This hypothesis, however, depends on the presence of a strong direct association of fat intake with coronary heart disease. Since we found no such association, competing mortality from coronary heart disease is very unlikely to explain our results." (They are being polite!)

The Women's Health Intervention USA trial whose result was published in 2006 involved 48,835 women studied over 8.1 years. It was a randomised intervention study with those in the experimental group receiving intensive counselling to reduce their fat intake (they were also counselled to increase their intake of fruits and vegetables to at least 5 servings daily and to increase grain consumption to at least 6 servings daily). By the end of the sixth year those in the experimental group were on average consuming 29% of their calories as fat (9.5% saturated fat) compared to 37% fat in the control (uncounselled) group (12.4% saturated fat). The result was no significant difference between experimental and control group in any of: Coronary Heart Disease or Stroke incidence, Coronary Heart Disease or Stroke Mortality or Overall Mortality (for references see Nabel, 2006).

The mainstream reaction to this result brings us to a *ne plus ultra* in ad hoc responses: the promissory note—give us time and we promise that we'll come up with something to explain these negative results. Dr. Elizabeth Nabel the head of the Heart Section of the US National Institutes of Health (which managed the Women's Health Initiative and hence this trial) said (*op cit.)* "There may have been some 'disappointment' that the studies didn't always give clear answers [in fact they gave clear answers, just not the ones that she and her colleagues expected/wanted]. The findings are what they are ... Now we are in a second wave of putting the findings into perspective [i.e. of trying to dream up some specific ad hoc response]."

In the meanwhile, despite the fact that the trial raised serious questions about the evidential basis of the NIH's dietary advice, the advice must it seems remain in force. Nabel pronounced *ex cathedra*: "The results of this study do not change established recommendations on disease prevention. Women should continue to ... work with their doctors to reduce their risks for heart disease including following a diet low in saturated fat ... ".

Before moving on to the different, though, of course, related theory 2, here for luck is just one more "paradox" facing theory 1: the "Japanese paradox". Japan is often described as having been the initial "poster boy" for the diet-heart hypothesis (essentially theory 1). In the late 1950s/early 1960s when the nutritionist Ancel Keys was first championing the hypothesis, Japan stood out as having the lowest animal fat intake of any country for which there were figures, the lowest average cholesterol level (it was 3.9 millimoles per litre compared to 5 mmol/L in the UK and 5.2 mmol/L in the USA) and by far the lowest rate of CVD and CVD mortality.

How much "proof" of the link between saturated fats and CVD could you want? Certainly, Keys himself needed nothing more.

Since that time however there have been significant changes in the Japanese diet involving a 400% increase in animal saturated fat intake. The average cholesterol level in Japan is now the same as in the USA (5.2 mmol/L). Theory 1 therefore seems to predict that the rate of death from heart disease in Japan will have risen since the early 1960s. In fact, it has *fallen* by 60%.[7]

One reaction to this was to claim that the Japanese have some special genetic feature that protects them against heart disease. This is again certainly ad hoc, but again testable; indeed, in this case, somewhat surprisingly, testable even in the absence of any specification of what particular genetic feature that might be. It predicts that Japanese émigré populations will have lower rates of CVD and CV deaths than the host populations. But again, this independently testable prediction is refuted: the Japanese community in the USA, for example, exhibits the same CVD and CV mortality rates as the US population as a whole.[8]

12.2.3 A Problem for Theory 2: Low *Cholesterol Causes CVD*

We now come to some "paradoxes" for, i.e. seeming refutations of, theory 2; which states, remember, that a high level of LDL-cholesterol in the blood, no matter how it got to be high, causes CVD.

A 2001 paper in *The Lancet* by a group of researchers from the University of Hawaii, Honolulu reported a study which found "increased mortality in elderly people [not with high but rather] with *low* serum cholesterol" (Schatz et al., 2001); emphasis supplied). Their data showed "that long term persistence of *low* cholesterol concentration actually increases the risk of death [by a whopping 65%!]. [Moreover], the earlier that patients start to have lower cholesterol concentrations, the greater the risk of death. These data cast doubt on the scientific justification for lowering cholesterol to very low levels." (You can say that again—though few in medicine have taken notice!) As these researchers pointed out, far from constituting

[7] In the same period, the rate of ischaemic stroke in Japan has plummeted by seven-fold. In the early 60s, Japan had the highest rate of strokes of any country (so, since ischaemic stroke is the other form of CVD alongside heart attacks, a little thought would have taken the sheen off its diet-heart poster boy image from the outset). So overall a 400% increase in saturated fat intake in Japan was associated with a near six-fold fall in overall CVD. (See Kendrick, 2007).

[8] Ueshema presents another possible ad hoc explanation for the "Japanese paradox"—that although cholesterol levels have risen in the Japanese population as a whole, they are still lower in the Japanese elderly than they are in the elderly in, for example, the US; and CVD, especially CVD mortality primarily of course afflicts the elderly. But this is hopeless: it would at best predict that the rate of CVD and CVD mortality would have remained roughly the same despite the overall increase in cholesterol levels in Japan, but not the actual fact that it fell dramatically. Moreover the explanation is in clear conflict with a series of studies that we will come to next, all showing that lowered cholesterol levels in the elderly is associated with an *increase* in CVD.

an outlier, their "data accord with previous findings of increased mortality in elderly people with *low* serum cholesterol". The Honolulu study was in fact the culmination of a series of studies, including reports from the Framingham project (which is generally seen as providing the initial basis for the high LDL-cholesterol/CVD link but many of whose original findings have been reversed by later research based on a much enlarged data set). All of these studies found that it was *low* cholesterol levels, rather than high ones, that were predictive of CVD in the elderly.

This certainly seems like a problem for theory 2 but there is an obvious escape route: maybe the elderly who have low cholesterol are a special case; maybe there is some further factor that affects them and which is the real cause of the higher rate of CVD and CVD mortality, where that factor also happens independently to cause a lowering of the LDL level. Again, although patently ad hoc, there is nothing inherently unscientific about this suggestion. On the contrary, a standard way of testing whether an observed correlation between factors A and B is genuinely causal is by checking that the correlation still holds when A is conditionalized on further factors C_n which might plausibly also be causes of B. So, for example, Hill and Doll provided strong evidence that smoking cigarettes causes lung cancer not simply by showing that there is an observable correlation between smoking and lung cancer, but by showing further that this correlation continues to hold when independent possible causes of cancer (such as, for example, living in an area with heavy air pollution) are conditionalized on. If, on the contrary, the correlation "disappears" conditional on C (that is, A and B are probabilistically independent given C) then that is evidence that the correlation between A and B is "accidental" and that, rather than A causing B (or vice versa), A and B are two separate effects of some underlying "common cause". (In the standard example, there is a definite positive correlation between having yellowed fingers and developing lung cancer but that probabilistic correlation "disappears" upon conditionalization on cigarette smoking: despite the strong probabilistic correlation, there is (of course) no causal connection between yellowed fingers and lung cancer, instead they are separate effects of the common cause: cigarette smoking.)

So, given the finding of a correlation between low cholesterol level and increased risk of CVD in the elderly, there is certainly nothing automatically unscientific about reacting by postulating that some other factor afflicts the elderly that "explains away" the observed low cholesterol/CVD link. And there's a fairly obvious candidate: the elderly often have comorbidities—maybe they come into these trials with some other (non-CVD) illness which *both* lowers their LDL-cholesterol *and also* independently predisposes them to develop CVD. This is undeniably ad hoc but we are learning that ad hoc is not a four-letter word. And indeed this suggestion is plainly testable: there should be a higher rate of comorbidities in the experimental arms of the trials that showed a correlation between low LDL-cholesterol level and high rates of CVD or CVD mortality. Moreover, it is known that certain diseases, – for example, advanced cancer and liver diseases such as chronic hepatitis B— *are* indeed associated with low LDL-cholesterol levels. However, people with comorbidities were excluded from all these trials—exclusions were based not just

on cancer and hepatitis but on any significant comorbidity. Testability but again refutation rather than confirmation.

Undeterred, Iribarren and colleagues sought to continue to defend theory 2 by in effect pointing out that any comorbidities had to be overt if elderly people were to be excluded from the trials on that ground. Perhaps, Iribarren postulated,[9] covert or subclinical illness was the common cause of low LDL-cholesterol and high rates of CVD—perhaps even as much as a decade (or more) before the illness became overt. Again ad hoc, again testable but again in conflict with the data. The Honolulu study, for example, reported (Schatz et al., 2001) that: "[in the light of our data] Irribarren's hypothesis is implausible and unlikely to account for the adverse effects of low cholesterol levels." (They too were being polite!)

Irribarren and colleagues also suggested that simple frailty (strongly associated with old age of course) might be a hidden common cause of low LDL-cholesterol and CVD. But a large Austrian study in 2004 found that the low LDL-cholesterol/CVD link is not in fact restricted to the elderly: "For the first time, we demonstrate that the low cholesterol effect occurs even amongst younger respondents, contradicting the previous [theories] ... that this is a proxy or marker for frailty occurring with age." (Ulmer et al., 2004).

Attempts to defend theory 2 are indeed looking like a degenerating research programme, but, in the (expressive if strictly logically ill-informed) words of the song, "you ain't seen nothing yet".

12.2.4 Another Problem for Theory 2: The "Female Paradox" and the Sex Hormone Hypothesis

Right from early on, it was recognised that the claim that high levels of LDL-cholesterol cause CVD faces a problem from facts about women. In general (though with some, independently interesting exceptions), across various populations, women have much lower rates of CVD than men; while—again in general though with some exceptions—women have much *higher* LDL-cholesterol levels.

Obviously, theory 2 predicts to the contrary that, given their higher LDL-cholesterol level, then, ceteris paribus, women ought to exhibit a higher CVD rate. This is a well-known problem for theory 2 with, however, you might think, a well-known solution: there must be some other difference between men and women that means that women are protected against CVD despite their higher cholesterol level; and the most obvious suggestion for that role, the most obvious biochemical difference between women and men, is their sex hormones.[10] So this is another

[9] Iribarren et al. (1995).

[10] It is true that women smoke less than men, but if you compare men smokers with women smokers or men non-smokers with women non-smokers you still generally find higher levels of LDL but lower rates of CVD in the women's groups.

of those "conflicting causes" saving hypotheses: it still may be correct that high LDL-cholesterol causes CVD and so women with their higher cholesterol level *would have* in general a higher CVD rate than men if other things were equal, but in fact at the same time, their distinctive sex hormones make other things in fact unequal, by somehow operating physiologically to lower CVD rates so as to more than compensate for the (supposed) effect of the high LDL level. Again: undeniably an ad hoc attempt to save the initial hypothesis, but again it is plainly testable.

The sex hormone hypothesis predicts, for example, that amongst women who have had hysterectomies, those who had their ovaries removed at the same time as their womb will, since they will no longer produce any sex hormones, have a higher rate of CVD than those women who only had their womb removed. But in fact, a 1963 study of several hundred woman already found no difference in the prevalence of coronary heart disease between those women who had had their ovaries removed as well as their womb and those who had had only their womb removed—both groups exhibiting a rate of 8% CVD some 15 to 20 years after their operation.[11]

A second clear prediction of the sex hormone hypothesis is that women who have been through the menopause should lose the protection allegedly afforded by their sex hormones, and so older women's rate of developing CVD should start to move up toward that found in males. Although this is widely believed to be true, scientific studies belied it. As early as 1987 a study found that "The normal menopause, which causes a gradual decrease in oestrogen production, was not associated with any increase in the risk of coronary heart disease."

A third prediction is that those women who take the contraceptive pill—which of course contains female sex hormones—should have a still lower rate of CVD than equivalent women not taking the pill. But the evidence is that women taking the pill in fact have *a greater* rather than reduced risk of dying from coronary heart disease (see, for example, Tanis et al., 2010)—even when other possible confounders, notably smoking, are controlled-for.

Perhaps the most famous prediction, however, made by the sex hormone hypothesis is still a fourth one: that women receiving Hormone Replacement Therapy (HRT) to counteract the negative effects of the menopause (or for some other reason) should exhibit lower rates of CVD (and CVD death) than equivalent women who are not on HRT. And, indeed, this looked for a while like being a first instance of Lakatosian *progress:* a 1983 observational study showed a 42% reduction in strokes and heart attacks in a cohort taking HRT compared to the average CVD rates amongst women of the same age not on HRT (Bush et al., 1983). This 42% is a *relative* risk reduction and so not as impressive as it might sound, but is still fairly substantial. And indeed, HRT became recommended treatment in the US on the basis of this study. However, as we will reflect in a moment, the result of this study was later completely overturned by a couple of large, reasonably high-quality randomised controlled trials which yielded an estimate of a 29% *increased* risk of

[11] Ritterband et al. in *Circulation,* 1963, **27**, 237 (reported in *The British Medical Journal*, Dec 14 1963, 1487).

CVD in those undergoing HRT. The official guidelines were promptly changed to recommend against HRT as a treatment aimed at reducing the risk of CVD.

This is one of the turnarounds (42% *protection* yielding to a 29% *increased risk*) that are often cited as showing that you can "never trust" an observational study. The correct view is, however, surely that you shouldn't trust the outcome of an observational study if a moment's reflection would suggest, on the basis of background knowledge, that the study was likely be multiply confounded. The women who were involved in the "treatment arm" of the observational study and therefore had chosen themselves to take HRT before it became mainstream treatment formed a self-selected and very special group: particularly fitness- and health-conscious, predominantly middle class and well-educated, containing very few smokers and so on; and hence should never have been thought of as representative of the general female population.

In any event, our latest ad hoc hypothesis was indeed eventually subjected to rigorous tests via a couple of large randomised trials. One of these was the **H**eart and **E**strogen/Progestin **R**eplacement **S**tudy (**HERS**). HERS ran for 6 years from 1998 to 2004 (various interim results were published during that period) and ended up involving 2763 women all of whom had a history of heart disease. Those women were randomised to either HRT or placebo. The outcome variables were either non-fatal MI (myocardial infarction) or death from CHD (coronary heart disease). The outcome was 172 fatal or non-fatal cases of heart disease in the HRT group compared to 176 in the placebo group. Of course, this is a tiny difference in such a large sample; and, moreover, there was actually a 24% *increase* in fatalities in the HRT group compared to placebo (compensated for by a 9% decline in the HRT group in the more numerous non-fatal events to produce the final barely distinguishable overall numbers). The study concluded "Based on the finding of no overall cardiovascular benefit [combined with notably more negative side effects in the HRT group] ... the investigators do not recommend starting this treatment for the purpose of ... prevention of [CVD]." (Hulley et al., 1998). Ad hoc theory (female sex hormones protect against CVD and therefore cancel out the (alleged) effect of the higher average LDL-cholesterol amongst women); is testable (women taking HRT should have a lower heart disease rate than equivalent women not taking HRT); but the test result is entirely negative; and so again a case of degeneration.

Another even larger randomized controlled trial on the effects of HRT ran for over 5 years and was published in 2002. This was a further trial under the auspices of the US Women's Health Initiative and looked at the effect of HRT not just on heart disease (as HERS did) but on CVD more generally—so including fatal or non-fatal ischaemic strokes. The result of this larger trial could hardly have been more definite: "[A]fter 5.2 years, there was a 29% *increase* in coronary heart disease risk, including an 18% increase in risk of CHD (coronary heart disease) mortality and a 32% increase in risk of nonfatal myocardial infarction in the HRT group. There was a 20% *increase* in the risk of fatal stroke and a 50% increase in the risk of nonfatal stroke in women assigned to HRT." (Writing Group for the Women's Health Initiative Investigators 2002; emphases supplied.)

12.2.5 The Switch to the Theory that "Good Cholesterol" Protects Against CVD

So, lots of ad hoc but testable hypotheses aimed at saving theory 2 but all of them immediately refuted. However, defenders of the theory were a far from fainthearted bunch and were certainly not ready to roll over just yet. Some of them began, for example, to argue that the sex hormones response to the "female paradox" had always been the wrong response. While it is true that women generally have higher levels of either LDL or total cholesterol and yet lower CVD levels, perhaps they also have higher levels of HDL-cholesterol. Several researchers had suggested that, in complete contrast to LDL ("bad cholesterol"), high rates of HDL may actually be protective against CVD (and hence count as "good cholesterol"). So perhaps it is their higher levels of HDL, rather than their sex hormones that reduce women's rates of CVD.

Well, same story—certainly ad hoc, but definitely testable. So, for example, since in the HERS study the average level of HDL-cholesterol was observed to be higher in the HRT group compared to placebo, this new HDL hypothesis predicts that CVD rates should have fallen in that group. Instead, as noted earlier, the rate of CVD mortality actually increased.[12] There was similar lack of confirmation in other studies. A large Russian study published in 1994, for example, reported "... there was no association of HDL cholesterol with mortality in Russian women." Despite the fact that the name "good cholesterol" somehow lives on (as the ghost of what ought to be a departed theory?) there seems to be no serious evidence that high HDL is protective against CVD.

Attempts to provide such evidence have unsurprisingly been made alongside attempts to develop drugs that raise HDL-cholesterol levels and so, if the HDL hypothesis were correct, would reduce the risk of CVD. The main group of such drugs to be tested were the "rapibs". The first of these was Torcetrapib. In tests, Torcetrapib raised HDL levels by around 60%; sadly, it also raised overall morality by almost 50% and was never approved for use. Delcetrapib had no effect on either LDL level or CVD. Tests on Anacetrapib provided evidence of a small positive effect but so small that Merck decided not to market it. (http.//www.pmlive.com/pharma_news/cetp_inhibitor_class_finally_dies_as merck_abandons_anacetrapib_1208239—see Kendrick 2018, p. 107).

However, the most interesting case is that of Evacetrapib. A very large study showed that this drug managed to more than double HDL levels (120% increase), it also lowered LDL by 37%—significantly more than statins manage. So, here's the next blockbuster, right? Unfortunately not: in tests Evacetrapib had zero effect on CVD.[13] As Steve Nissen, a celebrated cardiologist and head of The Cleveland

[12] See again Hulley et al. (1998).

[13] https://www.forbes.com/sites/matthewherper/2015/10/12/eli-lillys-good-cholesterol-goes-bad/#47d83c527de8.

Institute in the US, wrote "the results can't be explained because the study was too small or because too few heart attacks and strokes occurred. The drug didn't work." This looks like a severe blow both to the hypothesis that raising HDL protects against CVD and also to the hypothesis (our theory 2) that lowering LDL protects against CVD.

Nissen was, however, firmly attached at least to the latter hypothesis. Having decided that the negative test result concerning Evacetrapib could not be questioned, Nissen therefore had to find another explanation of the fact that LDL levels had gone down substantially but CVD rates were not affected. "There are" he wrote "two hypotheses to explain the results". One of these was that "lowering LDL cholesterol was beneficial but something else evacetrapib did causes toxicity [so as to outweigh the supposed good effect of the lowered LDL]". The other was that "it matters *how* you lower LDL cholesterol". (I perhaps do not need to point out that there is a third explanation: viz. that lowering LDL-cholesterol has no effect on CVD. But, as noted, Nissen could not bring himself to countenance this possibility.) So CVD risk *is* lowered by lowering LDL levels, but some ways of lowering LDL are ineffective even though that is not because they trigger some other mechanism that outweighs the alleged benefit of the lowered LDL.[14] This seems to be another maximum in untestable adhoccery. Since there are no signs to pick up of interfering processes (that's the first possible hypothesis which Nissen dismisses), presumably the only way to tell if someone's cholesterol has been lowered "in the right way" is by seeing if they develop CVD; if they don't develop CVD then their LDL was lowered in the right way; if they do develop CVD, it was lowered in the wrong way.

Finally, turning back from theory 2 to the HDL/"good cholesterol" hypothesis generated to protect it, a further interesting twist in the story originated in the picturesque Italian lakeside village of Limone sul Garde. A family living there was identified, all descendants of one man—Giovanni Pomarelli—born in the village in 1780. Both the family history and the current family (consisting of some 40-odd souls) had been extensively studied as the family exhibited amazing longevity and, especially, exceptional immunity to heart disease. The cholesterol levels—in particular the HDL levels—of the current members of the family had been carefully measured. Despite their immunity to heart disease, their average HDL level (and HDL is, remember, supposed to be protective against heart disease) was remarkably low—*much* lower than the Italian population average. Ah!, but what is special about this family is that all carry a genetic mutation, inherited from Giovanni Pomarelli, which produces a distinctive form of the apolipoprotein that holds the HDL and the fatty particles together to form the HDL-cholesterol lipoproteins that circulate in the blood. This distinctive form of the HDL apolipoprotein was dubbed "ApoA-1 Milano". (It was first identified and analysed in laboratories in Milan.) Perhaps, although standard HDL-cholesterol is indeed the more protective against CVD the higher its level, ApoA-1 Milano HDL is, by contrast, a very special case and

[14] https://mdedge.com/ecardiologynews/article/108182/lipid-disorders/accelerate-evacetrapibs-clinical-failure-sinks-lipid.

is protective no matter what its level—maybe even the lower its level the more protective it is.

So we have layers of adhoccery here. The theory that high levels of HDL are protective against CVD was originally produced as an ad hoc response to the "female paradox" difficulties for theory 2 (and the lack of success of dealing with those anomalies via the sex hormone route). Then that HDL theory was itself put into empirical difficulties and the ApoA-1 Milano hypothesis was an ad hoc response to those difficulties. But layered or not, the hypothesis is again testable—at least in principle. The most direct test would be via genetic engineering: give initially normal people the Apo-A1 Milano variant HDL and see if they exhibit lower rates of CVD and CVD mortality. But this was something, if at all, for a date far in the future. Perhaps, it was conjectured, if people were injected with Apo-A1 Milano HDL, they would exhibit at least *some* reduction in CVD risk.

A pharmaceutical company called Esperion Therapeutics obtained a patent on the production of cloned Apo-A1 Milano HDL; and some small initial trials, using the proxy marker of reduction in the volume of arterial plaque, along with some animal experiments were trumpeted as 'amazingly' positive. However, it was clear that producing convincing evidence of an effect of these injections on CVD rates in humans would require a very large trial—one affordable only by a BigPharma giant. And Pfizer in fact duly bought out Esperion with the sole motive of thereby acquiring the patent on Apo-A1Milano HDL and of running that trial (and of course with a view to reaping the financial benefits if the trial was positive and Apo-A1 Milano injections became the new blockbuster treatment).

We do not know what the outcome of that large trial was (despite some regulatory efforts, pharmaceutical companies are able to keep very tight control on the data from trials that they fund and they release results only when convenient for them). However, I think we can infer just how negative that test outcome must have been: Pfizer paid $1.25 billion to buy Esperion Therapeutics and hence obtain the patent on Apo-A1 Milano; 5 years later, after running the trial, Pfizer sold the patent for $ 10 million. (This represents a loss of greater than 99% on their initial investment.)

The patent was bought by a company called The Medicines Company—a start-up that specialises in picking up treatments for which there was as yet no solid evidence, but which they judged still to be somewhat hopeful. The Medicines Company ran a further trial on Apo-A1 Milano—though, since they did not have the financial clout of Pfizer, this trial was again on a proxy marker (again atherosclerotic plaque volume) rather than on CVD itself. They did publish the result of this trial: "Percent atheroma volume decreased 0.94% with placebo and 0.21% with [ApoA1- Milano]". So Apo-A1 Milano was actually outperformed by placebo—albeit fractionally and on a by no means clearly meaningful proxy outcome.[15]

Unsurprisingly, nothing has been heard of Apo-A1 Milano since.

[15] For details of this whole story see https://www.science.org/content/blog-post/long-saga-apo-a1-milano.

In sum, then, the theory that a high rate of HDL-cholesterol is protective against CVD was born as an ad hoc response to a difficulty for theory 2, the difficulty being that women generally have higher rates of LDL-cholesterol and yet at the same time lower rates of CVD than men; the initial ad hoc attempts to explain this difficulty, via the sex hormones hypothesis, produced significant degeneration, so there was a switch to the theory that it is HDL, not female sex hormones, that is protective; that theory is itself testable in a number of ways—all of them in fact being met by immediate refutation. Degeneration piled on degeneration.

12.3 The Clash Between What Ought to Have Happened and What Actually Happened

To reiterate my earlier concession: I do not claim to have looked at all the different responses that have been made in the research literature to difficulties for theories 1 and 2 and how those responses have fared evidentially—let alone, of course, at all possible responses, of which there are clearly indefinitely many. A series of degenerative steps does not entail that a programme overall has degenerated beyond hope of redemption; and Lakatos, remember, was always keen (I believe, too keen) to stress that a degenerating programme, no matter how degenerate, might "always stage a comeback". Nonetheless, the above does, I suggest, form a reasonably telling case that both of the mini-programmes at issue have degenerated sufficiently to call for the rejection of the two hypotheses in whose defence those mini-programmes were built. Especially since there seem to be no instances of empirical progress produced by either programme to balance against the degenerative steps.

However, instead of being rejected on the basis of this degeneration, theory 2 is still very much enshrined in medical orthodoxy: everyone is urged by the medical profession to 'know (and frequently check) their number', i.e. their LDL-cholesterol level and immediately treat it—by taking statins—if it is "high", in the expectation that by reducing their LDL-cholesterol level, the statin will, in accordance with theory 2, in turn reduce their risk of developing CVD. Millions and millions of people worldwide are taking statins life-long in the firm, and medically endorsed, expectation that it will reduce their chances of suffering from cardiovascular disease. (And the cholesterol level that counts as 'high' keeps on being lowered.) As for theory 1, there was until recently a similarly firm consensus that the uniquely healthy diet is one low in saturated fats; and hence that reducing the amount of saturated fat in your diet and replacing it with "healthy" carbohydrates and unsaturated fats was a sure way to reduce your risk of developing either a stroke or heart attack. The programme to defend theory 1 had definitely begun to degenerate long before this consensus began to be (rather reluctantly and very patchily) questioned.[16]

[16] See, for example, Harcombe et al. 2016.

This clash between what you might expect to happen on the basis of the Methodology of Scientific Research Programmes (MSRP) and what has actually happened (and is happening) brings us to another aspect of Lakatos's thought.

12.3.1 Internal and External History

In a much-discussed 1971 paper, Lakatos introduced the idea of "internal" and "external history". As Lakatos saw it, each methodology or philosophy of science endorses a narrative of how the history of science *ought* to have gone in terms of the acceptance or rejection of the available hypotheses at a given time, depending on the evidence available at that time. This is "internal history" which Lakatos famously also called a "rational reconstruction" of the history of science. In case the actual history differs from its rational reconstruction, the methodology supplying that rational reconstruction is, he went on to claim, obliged to provide an "external" historical explanation of the difference, where that external history should of course itself be empirically testable and empirically confirmed: "... when history differs from its rational reconstruction, [external history] provides an empirical explanation of why it differs." (Lakatos, 1971, p. 118). The underlying idea (Lakatos's "meta-methodology" for the appraisal of rival philosophies of science), then, was that a philosophy itself gets confirmational brownie points from the acceptance (or rejection) of a theory at a particular time if it *either* delivers the judgment that the acceptance (or rejection) of that theory at that time was rational (scientific/evidence-based) *or* it entails that the acceptance/rejection of the theory was not rational but there is a supplementary "external" historical account of the divergence between what ought to have happened and what actually did happen; where that "external" account is empirically confirmable and empirically confirmed.

While Lakatos argued that there have been any number of clashes between actual history and, for example, its naïve-falsificationist-reconstruction, the only clear example of a clash between actual history and its rational reconstruction in the light of Lakatos's MSRP that any of us could come up with at the time he was writing in the early 1970s was the "Lysenko affair" in Stalinist Russia. This involved the endorsement by some Russian scientists of Lysenko's half-baked neo-Lamarckian views about genetics (more specifically, plant genetics) over the orthodox neo-Mendelian approach of Lysenko's original mentor, Vavilov (along of course with that of all competent geneticists from the West). (See, for example, https://en.wikipedia.org/wiki/Trofim_Lysenko) This case, however, was not entirely satisfactory: in part because the "external factor" was so singular and obvious—Stalin took the view that Lysenkoism was altogether the "more Communist" approach and of course was in a position to ensure that his opinion was "influential"; and (mainly) because it is for that reason unclear how many of the Russian endorsements of Lysenkoism were genuine, rather than feigned with a view to political convenience and/or personal safety.

The medical example we have been considering, however, constitutes a further, and altogether more challenging case. There are, as we have seen, in this case sharp divergences between the internal history endorsed by MSRP and real history. And there is no serious doubt that the real opinions of medics and dieticians generate these clashes. The defender of MSRP must, therefore, provide an "external history" to explain those clashes; and that external history should of course be firmly empirically supported.

I shall not attempt to develop here anything resembling a full external history of the attitudes toward theories 1 and 2. Instead, I shall just point to four factors that were clearly involved—introducing them in an acknowledgedly preliminary and sketchy way but saying enough, I hope, to indicate that they are all firmly based on evidence. I will deal with them in order of increasing importance.

First, the intuitive, one might almost say emotional, appeal of theory 1 is undeniable. It is difficult not to be repelled by the sight of large amounts of solid fat. All recoil from images of "fatbergs" blocking the London sewers. The physiological counterpart seems so natural: despite our better selves, we eat fat, and so have fat in our blood stream; fat can get deposited on artery walls and eventually block them. Eating animal fats *must* be doing us harm—it "stands to reason". (This despite the facts that: (i) the atherosclerotic plaques involved in CVD contain cholesterol (amongst other things) rather than fats; (ii) dietary cholesterol was very quickly abandoned as a cause of the plaques, even by the most vocal supporters of the Diet-Heart hypothesis; *and* (iii) it is not plaque blocking the artery that causes the MI or ischaemic stroke, but rather a blood clot that breaks away from that plaque and blocks an artery closer to the heart or brain than the artery on which the plaque was formed!). The intuitive appeal of the theory certainly seems to account for its uncritical acceptance by the general public and for how quick some were to accept guidelines for "healthy" (low fat) eating despite the lack of anything remotely resembling telling evidence. And it also seems to have played some role even amongst scientists.

Secondly, it is a well-known and often recurring phenomenon that scientists who have become associated with a particular hypothesis go on to defend it against attack almost as if they were being attacked personally—especially in "softer" sciences where effects are generally multifactorial and the impact of evidence therefore less direct. As Malcolm Kendrick puts it in his 2014 book *Doctoring Data* (p. 141):

> "When an expert is wrong, he, or she is far less able to change their mind than you. Because it matters so much more to them than anyone else. Their entire reputation, status and income may be built on the hypothesis they ... support."

A few charismatic individuals who fit this description and so are determined to defend a hypothesis at all costs may exert an inordinate influence on the attitudes of others. In the case of theory 1, the nutritionist Ancel Keys from the University of Minnesota was such an individual. Keys became the embodiment of the heart-diet hypothesis, becoming widely known as "Mr Cholesterol" and, for example, appearing as such on the front cover of *Time* magazine. Keys became very attached indeed to theory 1. He had, it seems, a very charismatic personality and

consequently attracted many followers. Having become famous as the champion of the theory, the length to which Keys was willing to go to defend its public standing is vividly illustrated by an episode that came to light only after his death.

Keys first became famous for his "Seven Countries Study" of 1957 which, for the seven countries he considered, pointed to a straight-line relationship between percentage contribution of saturated fat to the diet and incidence of heart disease: for those countries, the higher the fat intake, the higher the rate of CVD. Whether or not Keys consciously selected his seven countries to support his favoured theory, objectively speaking his study suffers from the worst sort of selection bias: it is not difficult to select a different set of seven countries for which the relationship goes in exactly the opposite direction—the higher the animal fat consumption, the lower the rate of CVD (see, for example, Kendrick, 2007, p. 63). It is unsurprising, therefore, that within scientific circles at least, Keys' study received at best a patchy, in fact predominantly cool reception and that the influential American Heart Association (AHA) refused to follow Keys' suggestion that it issue strong advice to adopt a low-fat diet as a means of reducing the risk of CVD.

Keys reacted to this initially cool reception of his work in two ways: first by getting himself and a co-defender of theory 1 elected to the relevant AHA Committee with a view to changing the judgement about "what the evidence shows" concerning fat in the diet—independently, if necessary, of any change in the evidence itself. (In this, he actually succeeded. We will consider the role of committees, guidelines and government directives very shortly.) Keys' other reaction to his initial disappointment was to begin to plan a large randomized blinded trial which, he assumed, would provide "gold standard" evidence that he had been right about saturated fat and CVD all along. He conducted the trial together with his Minnesota colleague Ivan Frantz. It involved a treatment group whose diet was modified to replace saturated fats with food items that have naturally high or artificially raised content of linoleic acid—an allegedly healthy polyunsaturated omega-6 fatty acid. Although the trial was completed in 1973, only a few snippets of the results were published (by junior members of the research team, including PhD students). Until, that is, in 2013 a group of Australian researchers discovered all the raw data and the analysis of that data in a set of cardboard boxes in the garage of the son of Keys' principal co-investigator, Ivan Frantz. The newly discovered results showed (a) a statistically significant lowering of serum cholesterol levels in the intervention (polyunsaturated) group; *but* (b) no effect of the cholesterol-lowering on either mortality from coronary heart disease or all-cause mortality. (In fact, and to the contrary, the trial found a 22% *higher* risk of death for each 30 mg/dL reduction in serum cholesterol (mg/dL is milligrams per decilitre, the preferred unit in the US—30 mg/dL is equivalent to 0.78 mmol/L (millimoles per Litre) in European units). Keys was the lead investigator and must surely have been complicit in the "burying" of these results (which of course tell strongly against theory 2 as well as theory 1). Keys was indeed *very* determined not to see his favoured hypothesis undermined in scientific and public estimation.

A few charismatic individuals with total devotion to a theory can, it seems, persuade surprisingly many others.

An important *third* element of our "external history" is the role played by advice from influential professional bodies and more especially guidelines issued by governmental bodies. As just noted, in 1957 after the publication of Keys' "Seven Countries Study", the American Heart Association (AHA) resisted strong pressure from Keys and his supporters and found that "The evidence does not convey any specific implications for dietary changes." (quoted from Le Fanu, 2018, p. 66) Keys responded by getting himself, and also Jeremiah Stamler his great ally in the fight for the acceptance of theory 1, elected to the relevant Committee of the AHA. That committee fairly promptly recommended a reduction in saturated fat in the diet with a view to (allegedly) reducing the risk of heart disease-, while admitting that there was, as yet, "no final proof". Thereafter the AHA has continued to play a major role in propounding ever stronger advice to the US population to avoid saturated fats and replace them either with carbohydrates or unsaturated fats—despite the fact that the prospect of "final proof" receded further and further in the light of negative results.[17]

As for theory 2, the AHA also, over the years, issued ever stronger advice to be aware of your cholesterol level and, if that level was "high", treat it by either dietary change or by taking statins. And a similar and still more influential role was played by a US government body. The National Cholesterol Education Program (NCEP), a programme managed by the National Heart, Lung and Blood Institute, itself a division of the National Institutes of Health was set up in 1985 and continues to operate. Its goal, according to Wikipedia, is "to reduce increased cardiovascular disease rates due to hypercholesterolemia (elevated cholesterol levels)" in the USA—a goal which, of course, inextricably ties the program's very existence to the truth of theory 2. The guidelines the NCEP supplies for correct medical practice—fundamentally the LDL-cholesterol level at which to institute statin treatment—in effect have the force of law: a medical practitioner can be successfully sued for malpractice in the USA if s/he contravenes those guidelines. It is difficult for a medical practitioner to question the evidential basis of a claim if by questioning it they might end up in court.

The NCEP's guidelines amount to interference in the practice of medicine to encourage (really mandate) application of theory 2. Such interference is by no means confined to the USA. In the UK, for example, the QOF (Quality Outcomes Framework) was introduced in the NHS in 2004. Regarded by many acute observers as having proved to be a major mistake, the QOF makes general practitioners' pay dependent on the extent to which they meet certain outcome targets. One of these is the number of patients whose cholesterol level they have measured and (if regarded as high) treated. Des Spence, a Scottish GP and regular writer for the *British Medical Journal,* estimates that over the first 10 years of its existence, the QOF had produced 3 million extra statin users (without any discernible effect on CVD rates). (See Spence, 2013). Again, it is not easy to be analytical about the real evidential basis of

[17] See the study headed by Salim Yusuf reported in https://www.medscape.com/view-article/884937#vp_3, as well as Harcombe et al. 2016.

a theory, if that claim is governmentally endorsed and your income depends (albeit in part) on applying it.

So far, our (outline) external history has been very much Hamlet without the Prince. The *fourth* and overwhelmingly most powerful influence in promoting theories 1 and 2, despite what I claim is their extremely poor evidential record, has been money—massive amounts of money from the Sugar lobby as regards claim 1 and even more massive amounts from Big Pharma regarding claim 2. Here I concentrate just on the latter.[18]

In 1976, Henry Gadsden, the Chief Executive Officer at Merck, then the world's largest pharmaceutical company, gave an interview to *Forbes* magazine in which he bemoaned the fact that his company only sold to those who were sick. He wanted instead to be able to sell to everyone: sick or well—"just like Wrigley's sell chewing gum". It might be thought that Gadsden was joking, but the fact is that in the 40 years between his making that remark and 2016, pharmaceutical company profits increased by 40fold—most of that due to the vast increase in the sale of drugs to treat risk of developing an illness rather than an actually developed illness (Le Fanu, 2018).[19] Of course, by far the main risk treated was the risk of developing CVD and the (allegedly) risk-reducing drugs were statins. Within a couple of years after its approval for use in 1987, lovastatin (sold under the trade name 'Mevacor' in the USA and the first statin to be given FDA-approval) was generating as much revenue as Merck's entire drugs portfolio a decade earlier. Statins have been the blockbuster drugs to beat all blockbusters. At peak (things have quietened down a little of late as the statins progressively come off patent), statins as a whole were bringing in an estimated $5 billion per annum in profits and it is estimated that total profit from all statins has been upwards of $1 trillion. The selling point of statins is of course that they reduce cholesterol levels; and, crucially, that by reducing cholesterol they reduce CVD risk. It would therefore be difficult to overstate the extent to which "Big Pharma" has been dependent for its profitability on the acceptance of the truth of theory 2.

So, over the past several decades, Big Pharma has certainly wanted theory 2 to be accepted as true. And the extent to which "What Big Pharma wants, Big Pharma gets" can be gauged by reading Ben Goldacre's 2012 *Bad Pharma: How Drug Companies Mislead Doctors and Harm Patients*, and, especially, Marcia Angell's 2004 *The Truth about the Drug Companies: How they deceive us and what to do about it*.

[18] The Sugar lobby (fruit juice and soft-drink manufacturers as well as table sugar), along with manufacturers of "healthy fat" products, such as Unilever who manufacture Flora margarine—an allegedly more healthy replacement for saturated-fat-replete butter)—have of course a vested interest in seeing saturated fat branded unhealthy since it keeps sugar out of the frame. A good place to start reading about their influence is Chap. 12 of Kendrick 2018.

[19] See also Part Three of Greene [2007]—Greene does not question the medical orthodoxy (that high LDL-cholesterol causes CVD) but nonetheless supplies much fascinating detail of the history of statins.

Sadly, medical research largely exemplifies "The Golden Rule" ("He who has the gold, makes the rules"): The Pharmaceutical Companies have an enormous amount of control over what medical research gets done, how it gets done, which results get published and which do not, and even what the results of the research are declared to be to an extent that is both staggering and frightening. Marcia Angell—no radical, anti-establishment figure but instead a former Editor-in-Chief of *The New England Journal of Medicine* (the world's most prestigious medical journal)—wrote "It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as an editor of *The New England Journal of Medicine*." The main reason for this was the influence of Big Pharma, not only in controlling research and publication of research results, but also in affecting medical opinion; and, as Angell points out, it exerts this influence largely through *money:*

> "No one knows the total amount provided by drug companies to physicians, but I estimate from the annual reports of the top 9 U.S.-based drug companies that it comes to tens of billions of dollars a year in North America alone. By such means, the pharmaceutical industry has gained enormous control over how doctors evaluate and use its own products."[20]

Here is just one illustrative example directly relevant to our cholesterol case: The decision taken by the National Cholesterol Program in 2004 to lower the point at which a person's LDL-cholesterol level starts to count as high, and therefore at which statin treatment is recommended/mandated, meant that millions more Americans were declared to have a high LDL-cholesterol level and were duly prescribed statins. This in turn of course resulted in tens of billions of extra profit for the drug companies. The financial interest statement for the 8 members of the Committee who made this decision (aside from the Chair who was employed by the National Institutes of Health and not allowed any overt connection with the drug industry) showed just short of 70 individual financial conflicts of interest—in terms of research and travel support, honoraria, consultancy fees and the like paid to them by companies directly involved in manufacturing and selling statins.[21]

To summarize: this section of the paper has considered the *prima facie* surprising clash between what Lakatosian methodology would have predicted would happen to theories 1 and 2 and what has in fact happened to them in contemporary medicine. I hope that I have at least indicated that a plausible, external, evidence-based explanation of that clash can be constructed. This in turn lends weight to the view that the negative appraisal of the evidential basis of theories 1 and 2 that I have argued is supplied by MSRP is correct; and that therefore both currently

[20] I should add that Angell does not accuse the medical experts of being directly bribed into endorsing claims that they do not really believe. (This is not a rerun of the Lysenko Affair with Big Pharma playing the role of Stalin!) The influence is much more covert and subtle—akin to the way that advertising clearly works (why else would financially successful companies spend so much on it?) despite the fact that (nearly) everyone insists they take no notice of it.

[21] See Kendrick (2014) pp. 160–161.

accepted official dietary advice and currently accepted medical practice in this area are in urgent need of reform. If this view were to be absorbed, it would be a truly significant case of Lakatosian thought having an impact outside of philosophy.

References

Bush, T. L., et al. (1983). Estrogen use and all-cause mortality. Preliminary results from the Lipid Research Clinical Program follow-up study. *JAMA, 249*(7), 903–906.

European Heart Network and European Society of Cardiology. (2012). *European Cardiovascular Disease Statistics 2012 Edition* September 2012. https://www.bhf.org.uk/plugins/PublicationsSearchResults

Feyerabend, P. K. (1975). *Against method*. New Left Books.

Gosse, P. H. (1857). Omphalos: An attempt to untie the geological knot. *BioScience, 48*(10), 848–850.

Greene, J. A. (2007). *Prescribing by numbers. Drugs and the definition of disease*. Johns Hopkins Press.

Harcombe, Z., et al. (2016). Evidence from randomized controlled trials does not support current dietary fat guidelines: A systematic review and meta-analysis. *Open Heart, 3*, e000409.

Hulley, S., et al. (1998). Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease. Heart and estrogen/progestin replacement study (HERS) research group. *JAMA, 280*(7), 605–613.

Iribarren, C., et al. (1995). Low serum cholesterol and mortality: Which is cause and which is effect? *Circulation, 92*(9), 2396–2403.

Kendrick, M. (2007). *The great cholesterol con. The truth about what really causes heart disease and how to avoid it*. John Blake.

Kendrick, M. (2014). *Doctoring data. How to sort out medical advice from medical nonsense*. Columbia.

Kendrick, M. (2018). *A statin nation. Damaging millions in a brave new post-health world*. John Blake.

Lakatos, I. (1971). History of science and its rational reconstructions. In R. C. Buck & R. S. Cohen (Eds.), *PSA 1970, Boston studies in the philosophy of science* (Vol. 8, pp. 91–135). Reidel. (reprinted as chapter 2 of Imre Lakatos: *The methodology of scientific research Programmes. Philosophical papers, volume 1* edited by John Worrall and Gregory Currie, Cambridge university press, 1978).

Law, M., & Wald, N. (1999). Why heart disease mortality is low in France: The time lag explanation. *British Medical Journal*, 1999. http://www.xcbi.nlm.nih.gov/pmc/articles/PMC1115846/

Le Fanu, J. (2018). *Too many pills. How too much medicine is endangering our health and what we can do about it*. Little, Brown.

Nabel, E. G. (2006). The Women's health initiative. *Science, 313*(5194), 1703.

Ried, K. (2016). Garlic Lowers Blood Pressure in Hypertensive Individuals, Regulates Serum Cholesterol, and Stimulates Immunity: An Updated Meta-analysis and Review. *The Journal of Nutrition, 146*(2), 389S–396S. https://doi.org/10.3945/jn.114.202192

Schatz, I. J., et al. (2001). Cholesterol and all-cause mortality in elderly people from the Honolulu heart program: A cohort study. *The Lancet, 358*(9279), 351–355. https://ncbi.nlm.nih.gov/pubmed/11502313

Spence, D. (2013). Kill the QOF. *The British Medical Journal, 346*, f1498. http://www.bmj.com/content/346/bmj.f1498

Tanis, B. C., et al. (2010). Oral contraceptives and the risk of myocardial infarction. *New England Journal of Medicine, 345*(5), 1787–1793.

Ulmer, H., et al. (2004). Why eve is not Adam: Prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. *Journal of Women's Health, 13*(1), 41–53. https://www.nvbi.nlm.nih.gov/pubmed/15006277

Writing Group for the Women's Health Initiative Investigators. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. *JAMA, 288*(3), 321–333. https://jama.jamanetwork.com/article.aspx?articleid=195120