Lamarck Will Not Lie Down

Certain experiments on mice have been claimed as evidence of Lamarckian inheritance. Attempts to repeat them have failed. Who is correct?

In early June Edward Steele, a young Australian immunologist, left England for his native soil, deeply embittered by what he perceives as haughty and unfair treatment by English academia. For the past 15 months, part of which time he was working at the Clinical Research Centre in London, he has been arguing vociferously that he has firm experimental evidence for a Lamarckian mode of inheritance, that is, inheritance of acquired characteristics. Many scientists who were drawn into the debate are now breathing a sigh of relief at the departure of a man who, they believe, has abandoned normal standards of scientific investigation through being too emotionally wedded to a pet hypothesis.

The Steele saga has passed across the pages of respected scientific journals; it has been aired on British Broadcasting Corporation (BBC) radio and television; and it has been promulgated in popular magazines and newspapers. The tone of the exchanges between participants caught in the debate became increasingly acerbic and the matter of discussion ever more tangled in nit-picking detail. Passions have run high.

The events of the past year or so have been billed as a confrontation between heterodoxy (Steele espousing his Lamarckism) and orthodoxy (the establishment standing by its Darwinism).

They have been described as the outcome of the tactless challenge of a raw young postdoc against the mature work of stuffy English professors. Accusations of inappropriate handling of data have been legion. But at the base of it all, however, is one apparently simple question: Can certain surprising and interesting results obtained in one laboratory be reproduced independently in another? The answer is proving more difficult to settle upon than might have been expected.

Claims for examples of Lamarckian inheritance were common in the 19th century, and they have continued to appear sporadically during this century. The notion that an advantageous characteristic, such as larger than normal muscles, that develops during an animal's lifetime can be passed on to its offspring is at odds with the modern genetic theory of Darwinian evolution. In terms of underlying mechanisms, Lamarckism was first put beyond the pale by the German biologist August Weismann, who, in 1885, espoused his doctrine of the continuity of the germ plasm.

There is a barrier, Weismann argued, between the germ cells (eggs and sperm) and the cells of the rest of the body (somatic cells). The barrier, if it exists, prevents any genetic mutation that occurs in somatic cells from being communicated to the germ line and thence to the offspring. Any genetically determined variation in offspring, the argument runs, must arise exclusively from genetic changes in the germ cell genes. So far, experience indicates that Weismann's barrier is essentially intact. Nevertheless, many people who are unhappy with a Darwinian explanation of evolution have continued the search for a chink in the barrier.

Steele has developed a hypothesis that, he claims, offers a genetic mechanism by which the barrier might be breached. Soon to be published in the United States as a book, entitled *Somatic Selection and Adaptive Evolution*, the hypothesis is likely to add vigor to the current fashion of denigrating Darwinism.

"Although Darwinism may account to some extent for the diversity and abundance of cells or organisms," writes Steele, "there remains a suspicion that it provides no satisfactory explanation for our intuitive belief that there appears to be an element of 'directional' progress in the complexity and sophistication of adapted living things." Steele sees "an undercurrent of Lamarckian modes of inheritance" as providing the directional element he seeks in evolution. Steele is also in search of, as he sees it, a better explanation of the speed with which evolution can advance and of the large coordinated changes that appear to be demanded. Some form of Lamarckism is again the answer. Steele's aim is not to replace Darwinism by his form of Lamarckism, rather he seeks "to enrich evolutionary theory" by adding a directional element to it.

Steele developed his answer—his somatic selection hypothesis—to these perceived problems during a short, intense period of activity toward the end of 1978. "The conceptual breakthrough came to me in July 1978 30,000 feet above the Atlantic," he says. "I was on my way to a conference in Germany and I was reading Arthur Koestler's *Janus*. It crystallized my ideas." The following week he joined his colleague Reg Gorczynski at a conference in Israel. "We gave our papers and then spent the rest of our time by the pool drinking beer and thrashing out the problems. I was really roaring along. I couldn't think of anything else. It's probably what eventually broke my marriage up."

Can certain surprising and interesting results obtained in one laboratory be reproduced independently in another?

Steele's commitment was complete. He spent many hours searching the literature "looking for evidence, looking for people who inadvertently had done the sorts of experiments I was thinking of." By October he had drafted a short paper that outlined the hypothesis. He showed it to a number of colleagues at the Ontario Cancer Institute, in Toronto. "Reg was delighted, but my supervisor, Al Cunningham, reacted negatively." The discouragement that Steele perceived from Cunningham was, he says, "the start of my problems." Nevertheless, he pushed on and within 2 months he com-

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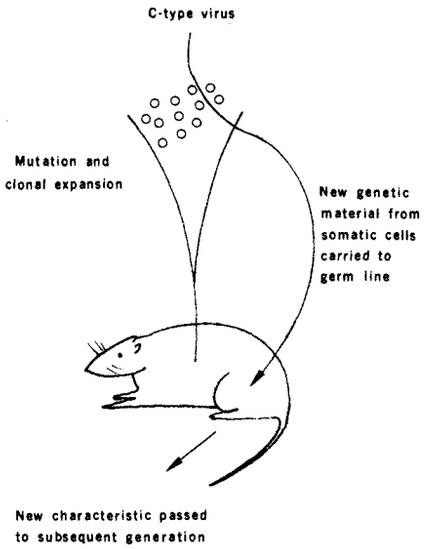
pleted the manuscript of what was to become his slim 91-page book.

The hypothesis is simple and at its heart is the idea that certain viruses, retroviruses, can carry genetic material from somatic to germ line cells. This notion is derived directly from Howard Temin's protovirus theory, which won him a share in the 1975 Nobel Prize for medicine. "In extreme cases," Temin wrote in 1971, "one could imagine that a product of protovirus evolution would infect the germ line, become integrated there, and thus affect progeny organisms."

In synthesizing his hypothesis Steele built onto Temin's remark the notion of somatic mutation and clonal expansion. During an organism's early life, Steele argues, mutations occur in the somatic cells, some of which may be better suited to prevailing environmental conditions. These cells will proliferate relative to their nonmutant relatives and will eventually dominate the organ. (An example would be liver cells that through mutation developed the ability to detoxify a harmful chemical present in some of the animal's food.) Because of the relative abundance of the mutant cells in the organism, there is a great likelihood, Steele contends, that retroviruses will pick up some of the new genetic material (probably as RNA rather than DNA), transport it to the germ line cells, and then insert it into the genome, whose role is to make the next generation. Steele even suggests that an important factor in the evolution of retroviruses is this ability to speed the evolution of their hosts.

Temin told *Science* that the hypothesis is tenable but that there is a major problem. "There is apparently no particular specificity in where the viruses insert their passenger DNA into the genome. This is obviously important for the hypothesis, and it therefore poses a severe difficulty." Another practical matter is the frequency with which transmission might occur between somatic and germ cells. Steele assumes transmission will be high. Temin says it is simply not possible to guess until more is known about the process, if it exists.

The book reflects the haste and enthusiasm that Steele brings to his work. He cites examples that apparently support his case, but ignores other equally valid interpretations. He indulges in flights of philosophy and imagination—for instance, he suggests that nucleic acid changes in our brains associated with our thoughts might find their way to the next generation—that are sketchily drawn. In a review of the book, Avrion Mitchison, an immunologist at University College, London, comments on its lack of critical examination and "the incomplete nature of Steele's argument." Mitchison also wonders how Steele would account for the observed genetic stability in populations if Steele's proposed system was a significant biological process.



Somatic selection hypothesis

Steele suggests that a mutant somatic cell favored by the environment will undergo clonal expansion. The altered genetic material from these cells will be picked up by C-type viruses which then might insert the material into the germ line genome, to be passed on to the next generation.

Such valid comments, and other important reservations about the hypothesis, have tended to be obscured by the flurry of events that coincided with its publication, first in Canada and then in the United Kingdom: Steele and Gorczynski claimed to have demonstrated Lamarckian inheritance in mice.

Steele had offered a manuscript of the book to a dozen or so people, including Temin, Sir Peter Medawar, Sir Karl Popper, and Arthur Koestler, and was receiving encouraging comments. Meanwhile Gorczynski was setting up an experimental system in which to test the hypothesis. This involved inducing a state of immune tolerance in one strain of mice by injecting into them cells of another strain, and then determining if tolerant fathers would sire tolerant offspring.

The classic work on tolerance was done in the early 1950's by Medawar (for which he received the Nobel Prize), Leslie Brent, and Rupert Billingham. And the classic way of demonstrating tolerance is to see if one animal will accept a skin graft from another strain whose cells were used to make the test animals tolerant. This is a tricky procedure that requires experience to produce reliable results. Gorczynski and Steele therefore decided to employ a laboratory test that measures the vigor with which an animal's spleen cells attack the cells of the donor strain. This cytotoxicity test is not without problems, a factor that loomed large in the debate that was subsequently to take place between Gorczynski and Steele and the London research group that attempted to repeat the work.

"We got our first results in February," recalls Steele. "I was stunned. It really worked. They supported the hypothesis." Steele, in his own words, was roaring. The data appeared to indicate that between 50 and 60 percent of progeny from tolerant fathers were also tolerant to the test strain cells. When these progeny bred, the frequency of tolerance was still substantial in the second generation, 20 to 40 percent, though there was some "waning" of the effect.

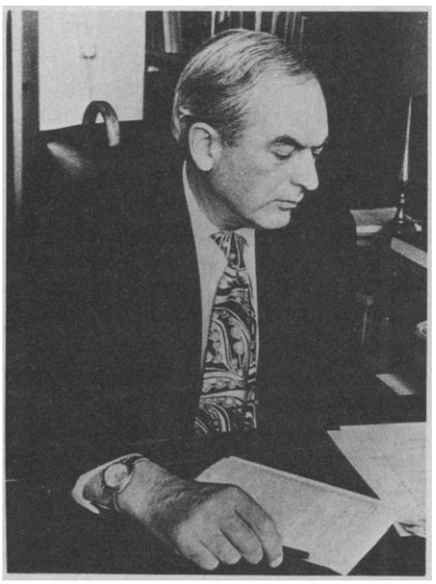
Thus, it appeared that animals that had acquired immunological tolerance to a specific test strain were able to pass on the characteristic to the next and subsequent generation at a high frequency: classic Lamarckian inheritance. And the fact that the trait was inherited through males rather than females cuts down, though probably does not eliminate, the possibility of transmission of important factors in the cytoplasm rather than the genes of the germ cells.

Emboldened by these distinctly heterodox results, Gorczynski and Steele extended their work by producing mice with immune tolerance to two separate strains. This is achieved simply by injecting the test animals with cells from the two chosen strains. Once again the question was, would these animals pass on their acquired tolerance to their offspring? And again the answer appeared to be yes. Moreover, although some offspring were tolerant to both strains, others were tolerant to just one of the strains. It seems that whatever was being passed to the progeny could segregate independently, just like separate Mendelian characters.

The results of the first experiment were submitted to the *Proceedings of the National Academy of Sciences* on 21 January 1980 (communicated, incidentally, by Howard Temin), and published in the May issue (p. 2871). Results of the second series of experiments are described in a paper submitted to *Nature* on 11 June 1980. Publication of this paper had to wait until the following February (vol. 289, p. 678), a delay that Steele now views as part of the academic community's attempt to discredit his work.

Steele had a 2-year contract with the

Ontario Cancer Institute and soon after embarking on his experiments with Gorczynski he began seeking a postdoctoral position elsewhere. "He was especially keen to go to London," says Cunningham. Through Cunningham's con-



Sir Peter Medawar

Medawar's work on immune tolerance in the early 1950's indicated that the acquired state was not passed on to offspring. He invited Steele to his laboratory in 1979 to pursue work that contradicted these earlier results.

tacts with immunologist David Dresser at the National Institute for Medical Research, London, Steele secured a Wellcome Research Fellowship to work in Dresser's lab. "I was happy to have Steele come here," says Dresser, "but I insisted that he spend most of his time on some conventional aspects of autoimmunity. I said he could devote 25 percent of his time to his inheritance of acquired tolerance project."

This was an offer Steele found easy to refuse. He was burning to pursue his revolutionary ideas, and Dresser's constraints would be just too much to bear. Medawar came to the rescue, prompted by Arno Mullbacher, a former colleague of Steele's, who was then working in Medawar's laboratory at the Clinical Research Centre. Medawar used his considerable influence to have the Wellcome fellowship transferred to the Clinical Research Centre so that Steele could concentrate on his chosen work, a move that was not without opposition. Medawar encouraged Steele to confirm and extend his observations.

While all this was going on the results of the first Gorczynski and Steele experiment were already causing a good deal of excitement. Data with implications as important as these had simply could not be ignored, but before they could be taken seriously, they had to pass through the filter of classic scientific practice: independent repetition in a second laboratory.

Elizabeth Simpson, who is part of Medawar's lab at the Clinical Research Centre, was particularly interested in the Gorczynski and Steele results. "If they were reproducible they'd be very exciting," she says. In September 1979, 7 months before Steele arrived in the laboratory, Simpson and her colleague Phillip Chandler set up their first attempt to repeat the experiment. Like Gorczynski and Steele, they used cytotoxicity testing instead of skin grafting to measure tolerance.

"It became clear that we didn't have adequate controls," recalls Simpson, "and there were one or two technical problems." Mullbacher, who at this stage was involved with the attempt to repeat the Gorczynski and Steele work, says that although two sets of these experiments showed no inheritance effect, a third did seem to be promising, from Steele's point of view. "I wasn't satisfied with the way the control and test analyses were scored," he says, "so these too should really be viewed as inconclusive."

Steele arrived at the lab in April 1980, toward the end of this first attempt to repeat his experiment. "It was a psychological disaster area," he says. "The rumor was that there was nothing in the results to support my work. I wanted to see the data, but I didn't get them until almost two weeks after I arrived."

Although Steele was welcomed into the lab with tremendous goodwill—his friend, Mullbacher, confirms this—his first actions began a process of erosion that eventually was to escalate. "I replotted their data," explains Steele, "and it immediately became clear to me that a significant number of the progeny were tolerant to some extent." He told Simpson and her colleagues that they had misinterpreted their data. "They never forgave me for doing that."

The second attempt to repeat the Gorczynski and Steele work began during the summer, and this venture was joined by Leslie Brent, professor of immunology at St. Mary's Hospital Medical School, London. Brent brought the required skin grafting expertise to the project. "Although Elizabeth was very enthusiastic about the project, I have to admit I was a little skeptical," he says. "You see, I had done experiments of this sort with Medawar and Billingham in the fifties and we saw no evidence of inheritance of tolerance."

Brent and Simpson, together with Lee Rayfield, Walter Fierz, and Chandler, tested 193 progeny of tolerant fathers and 130 progeny of nontolerant fathers, using cytotoxicity analysis and skin grafting. Their results, which were submitted to *Nature* on 4 February 1981 and published just 2 months later (vol. 290, p. 508), "do not support [Gorczynski and Steele's results]." They also wrote, "We still believe that all experiments executed hitherto to corroborate the Lamarckian interpretation can be faulted."

This paper has been the focus of a somewhat rancorous dispute between Steele and the authors, even before publication. Although Steele was never to be directly involved in the attempted repeat—this would have violated the principle of independent replication—he understood that he would be on hand to offer advice and the benefit of his experience. But before very long Steele was excluded from close contact with the work and denied access to the data. Steele saw this as an attempt to isolate him. Brent explains that when appearing on a television program Steele had claimed that research at the Clinical Research Centre looked promising as support for his ideas. Steele committed the same "sin" at a scientific meeting. A great deal of anger was aroused over these incidents, and Brent, Simpson, and their colleagues felt they should no longer share their raw data with him.

Steele engaged in voluminous correspondence with many people, including Brent and Medawar. Sometimes the technical suggestions he made were followed, such as the use of hybrid rather than pure strain skin grafts, as these have a better chance of revealing partial tolerance in test animals. Mostly, his pugnacious style irritated. "You can't write letters like that to English professors," his close friend and scientific colleague, Jeffrey Pollard, told him. "This sort of thing probably finished me off," muses Steele.

The atmosphere in the lab was deteriorating rapidly. Steele felt that he was being obstructed in his work and that people were very negative to him. Simpson and her colleagues complain that they were unable to have a proper discussion with Steele because, they say, he would be abusive when contradicted. Bob Blanden, an immunologist at the John Curtin School in Canberra, has known Steele for several years and visited Simpson's lab in August last year. He

observes that "whenever a conflict arose there was very little diplomacy on either side."

Steele was invited to a seminar on 10 December at which the group met for the first time to consider the data that had accumulated over the previous 6 months. The group was fulfilling its promise to show Steele the data when the experiment was virtually complete, though there were some skin graft results yet to be collected. It was a tense meeting, chaired by Brent. "I saw it as an attempt to crush me," says Steele. Shortly after this seminar Steele visited Australia to look for a job.

At the beginning of October Steele had written a long letter to Medawar explaining the problems as he saw them from the day he arrived. "I asked him to get them off my back," he says. For some months Medawar had become increasingly disturbed by the turn of events in the lab, and he had repeatedly encouraged Steele to devote at least some of his time to projects other than the somatic selection hypothesis. He also said that although it is difficult and painful to tear oneself away from a favorite hypothesis, sometimes it just has to be done.

Toward the end of September Medawar wrote another note to Steele, once again to suggest that he should apply himself to some more conventional project. He also said that Steele should stop writing letters and drafting manuscripts. Attempts to steer him back to the laboratory were interpreted as attempts to block him. Even his friend Bob Blanden's entreaties in this direction were rebuffed. So, Medawar's reply to Steele's "get them off my back" letter was to say that his contract, which was to end in April 1981, would not be renewed.

When Steele returned from Australia at the beginning of February Medawar gave him a copy of the Brent-Simpson manuscript that had just been submitted to *Nature*. Steele decided that "the gloves were off" and penned a 25-page letter entitled "Criticism." It was a blunt document. "Clearly, much laboratory time has been put into this paper," he began. "Let me say, however, that *quality*, and *not quantity*, must be the main guiding light in scientific research." He conceded that the skin graft results were "beyond reproach and uniquivocal," and aimed all his barbs at the results of the cytotoxicity tests. "Shoddy and leaves much to be desired," is how he described some of the work. "The decision to push ahead and publish irrespective of data quality is not only *dishonest* but also *bloody-minded*," he concluded.

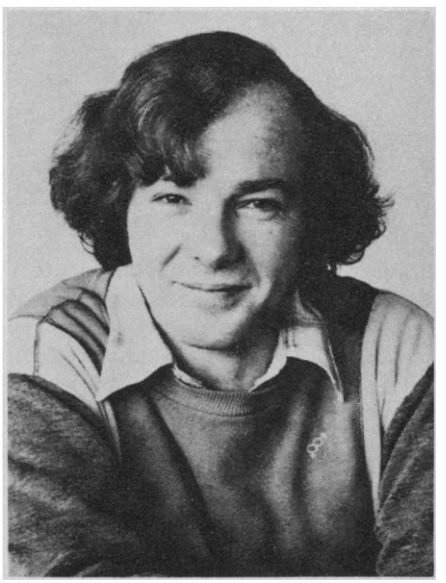
The document was not well received. Simpson trashed hers. Brent wrote a curt response.

Two weeks after Steele wrote his "Criticism" to Brent, Simpson, and their colleagues, his paper with Gorczynski was published in *Nature*, 8 months after it was first submitted. The paper was accompanied by an editorial: "Too soon for the rehabilitation of Lamarck." The editorial noted that the Gorczynski and Steele paper was heterodox and interesting but that failed attempts to repeat the work were soon to appear. The Brent-Simpson paper followed at the beginning of April.

That same April issue of *Nature* carried a second negative paper, this one by Simpson and her Clinical Research Centre colleagues and Anne McLaren at University College, London. This paper reported on tolerance induced by a different method. If two mouse embryos of different strains are fused at a very early stage, the product will be a single chimeric, or tetraparental, mouse. Inevitably, the mouse will accept skin grafts from either of the "parental" strains. The question is, will a single-strain offspring from such an animal be tolerant to the second strain that made up the parent? Will the tolerance induced in the chimeric adult be passed on to a single-strain offspring? The answer, according to McLaren and her co-workers, is no.

These results on tetraparental mice appear to be confirmed by a similar but independent experiment by Eric Nisbet-Brown and Thomas Wegmann at the University of Alberta. Their paper has just been submitted to the *Proceedings of the National Academy of Sciences*, communicated, ironically, by Temin.

Steele counters these results on the tetraparental animals by speculating that the type of tolerance they develop is different from that induced by neonatal injection of foreign cells. This brand of tolerance, he says, would not be passed on to offspring because it involves the deletion of certain immune cells, and the somatic selection hypothesis does not allow for the transmission of the absence of a character. "He didn't say that when he came through the lab last year," comments Nisbet-Brown. "He said he thought the experiment was a good idea."



Birgitte Nielson

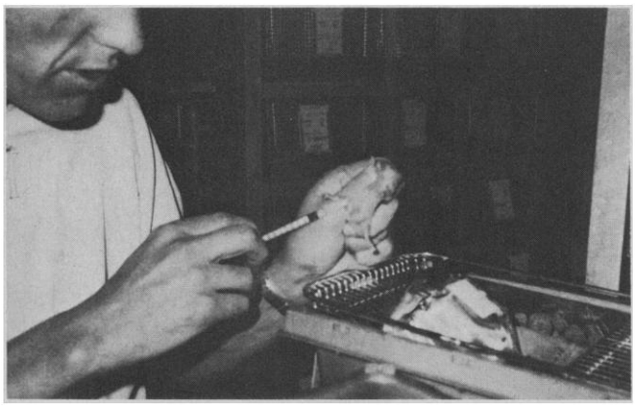
Edward Steele

Immunologist in search of an evolutionary hypothesis.

Most of Steele's criticism has, however, been concentrated on the Brent-Simpson paper, particularly on the variable nature of some of the cytotoxicity results. He also suggests that the fathers they used were not as tolerant as the ones that he and Gorczynski worked with. His reason for saying this is that Brent and Simpson's test fathers showed some response in the cytotoxicity analysis. Two points should be made here. First, Simpson's laboratory is one of the most experienced in the world for this type of analysis. Their tests frequently have a high degree of sensitivity that shows cytotoxicity even in tolerant animals. Second, Brent demonstrated their "solid tolerance" by skin grafting. "They held them firmly for more than a year," says Brent. "What more can you ask?"

In embarking on the repeat of Gorczynski and Steele's work, Brent, Simpson, and their colleagues did commit one serious error. They did not follow Gor-

Steele's paper, published in *Nature*, was accompanied by an editorial titled "Too soon for the rehabilitation of Lamarck."



Immune tolerance

Gorczynski and Steele inject 100 million cells of one mouse strain into newborns of another strain. This injection, repeated every 2 weeks, represents 10 percent of the newborn's weight.

czynski and Steele's protocol in every detail. Gorczynski and Steele report that they induced tolerance by injecting 100 million cells from their foreign strain (1:1, spleen : bone marrow) into neonatal mice every 2 weeks. By contrast the animals in the repeat experiment received 50 million cells (1:10, bone marrow : spleen). "There appeared to be good reasons for doing this at the time," says Simpson, "but it was a mistake." Brent admits it was "a serious error of judgement."

In circumstances such as these, a negative repeat experiment cannot conclusively be said to negate the original results unless the proceedure has been identical in every detail.

Steele now describes these two aspects of his regime as being of "fundamental importance." Brent, Simpson and her colleagues, however, express serious doubts about how rigidly Gorczynski and Steele stuck to the regime they describe in their papers. Steele apparently did not emphasize these points as being so crucial until the work was nearing completion and negative results were forthcoming. Nevertheless, Brent, Simpson, and their colleagues recognize their formal error and are already 5 months into yet another repeat experiment, this time with the regime for producing immune tolerance exactly the same as Gorczynski and Steele's. Results will be available in 2 to 3 months.

Meanwhile the story has taken its most bizarre turn yet. On 8 April Steele took part in a 30-minute BBC radio program, "Scientifically Speaking," on which he discussed his hypothesis and his work with Gorczynski. The interviewer, John Maddox, who is editor of *Nature*, was able to say at the end of the program, "As it happens the scientific journal *Nature* will be publishing tomorrow a report by some people at the Clinical Research Centre which describes how they've tried to repeat Steele's results and have failed."

If Steele believed himself set up on this program, he must have felt even more so 2 weeks later when on another edition of "Scientifically Speaking" he faced Brent and Jonathan Howard, a researcher from the Institute of Animal Physiology in Cambridge. Simpson also appeared in the broadcast, but her interview had been taped separately. The broadcast discussion was 45 minutes, but the recording lasted almost 3 hours. Toward the end Steele dropped a bombshell, or so he thought.

"I had been going through their paper some days before the recording," says Steele, "and I started to plot out their skin graft data. Suddenly I could see a scientific resolution to this whole issue. I was elated. Their data support our work. The test animals do hold onto their grafts longer than the controls." These were the data which in his "Criticism" letter he had described as "beyond reproach and unequivocal."

Before going into the studio, Steele told the program's producer that he might have a surprise, but he did not say what it was. "I hadn't fully decided that I would bring this out in the program," Steele says. "But as the recording went on it became clear that this was to be the final kill off for Steele. So I did." Uproar ensued, and the recording had to be brought to a temporary halt. Brent was extremely distressed at being thrust into this highly unusual way of handling scientific data, but he agreed to look at Steele's reanalysis and comment on it.

"Ted Steele has failed to take into account the sex of the animals," said Brent. This is crucial in comparing skin graft rejection, as females slough off grafts more rapidly them males. "So the results are totally meaningless. I think it shows a kind of overcommitment to a theory which forces Ted to make this kind of shallow analysis."

Steele's action thus backfired badly, and for the next few minutes of the broadcast he received a severe bruising on this and other aspects of his work. Steele complains that the tape was cut so as to make his position look worse than it was.

By now Steele was fully convinced that he was the target of a concerted assault. "If you look at it all," he says, "it was orchestrated to have maximum impact. The *Nature* papers (9 April), the radio programs (8 and 22 April), and the London meeting of the British Society of Immunology (10 April)." Brent described the results of the joint study at this meeting. "They knew I couldn't get to that meeting to defend myself," claims Steele. Simpson reports that Steele was in the laboratory for some part of that day and considers the complaint groundless.

Instead of bowing out at this point, Steele went back to the skin graft data and through a different form of analysis, in which he separated the males and females, he arrived at a statistically significant difference in the time the female test animals held their grafts. He also replotted the data for the males, dropping the data on the progeny of half the controls, and claimed that this result revealed a significantly large number of test animals with a slower than expected rejection of the grafts. Steele published the results of his reanalysis on 7 May in *New Scientist* (p. 360) under the title, "Lamarck and immunity: A conflict resolved."

Not surprisingly Brent, Simpson, and their co-workers did not consider this to be a resolution of anything. They too used the pages of *New Scientist* (21 May, p. 493) to reply to "the imputation that we lack in scientific judgement and statistical competence." They insist that correct statistical analysis of the female progeny does not show significance, and that "the male progeny of only one out of ten experimental fathers showed a slight prolongation of graft survival." Dropping the progeny of half the control fathers from the analysis is, they stress, totally unjustified. If all the animals are considered, they say, no statistical significance emerges.

Steele claims that a number of people confirm his reanalysis, including Howard, who had refereed the Brent-Simpson paper. "The graft data do show an effect in the direction Steele claims," he says. "I have to admit I didn't notice it previously, but it is very small. It is not clear whether it is statistically or biologically significant." Blanden comments: "Steele had to manipulate Brent's data

in an arbitrary way to show an effect. If you accept the manipulation as valid—and it's not clear that it is—then you do get a statistically significant result. It is, however, only marginal. I can't blame Ted for doing this. I'm sure I would have done the same in his position."

Inevitably there are at least an equal number of statisticians who claim that there is no significant effect to be seen. All of which confirms that when data are as close to the margin as Brent's clearly are, if you look hard enough you will see statistical significance if you want to. For the experimentalist, it confirms that the effect, if real, is small in this system.

In their *New Scientist* article, Brent and his colleagues press further the charge of data selection against Steele. They refer to "a previous communication to us" (the "Criticism" document) in which he excluded data from control animals on the basis that they had low cytotoxic activity, and therefore must be abnormal. "If this is done," they write, "it is hardly surprising that the progeny of tolerant fathers should seem hyporesponsive." Steele counters this charge by saying that "you can't do statistics until you first use common sense."

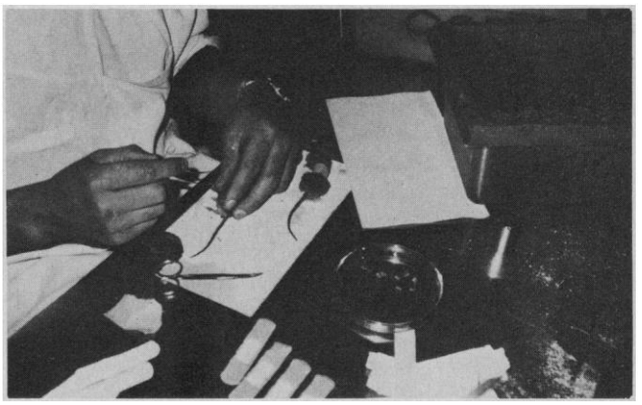
Work of this nature is typically done "blind" right through the computer analysis to eliminate subjective bias. While he was at the Clinical Research Centre, Steele declined to use the computer for his work, saying he felt uncomfortable with it. "He took his data home with him, together with a pocket calculator," says Walter Fierz, the laboratory's statistician. "This can be a problem," he suggests. Simpson says that data selection, plus some technical shortcomings she sees in Gorczynski and Steele's analysis, "could account for at least some of the differences between our results."

When he was not working on data or promulgating his hypothesis, Steele combed the literature for papers that seem to support his case. His list is now considerable. One case, which he cites in the *Nature* paper, is reported by Ronald Guttmann and Bradley Aust. In 1963 and 1964 they described the apparent inheritance of induced tolerance in mice, much like Steele's own work (except, interestingly enough, that they used spleen cells for induction of tolerance, not bone marrow that Steele now says is so crucial).

The Guttmann and Aust reports, like Gorczynski and Steele's, were quickly followed by a failed attempt to repeat the work. Steele does not mention this paper, which was by David Steinmuller, now professor of immunology at the Mayo Clinic. "No, I've never come across this paper," claims Steele.

Skin grafting

Mice in Gorczynski's laboratory that have undergone induction of immune tolerance accept skin grafts from the "foreign" strain. Do tolerant fathers pass on this ability to their progeny? Gorczynski now has evidence that they do—up to a point.



Guttmann now says of his work that "it is an interesting laboratory phenomenon, but how much further it goes is rather doubtful." Steinmuller's comment is, "I'm not willing to buy it as a reproducible phenomenon." Someone else who had trouble reproducing the effect is Willis Silvers, of the University of Pennsylvania. "Billingham and I tried it at the time," he says, "but we didn't get any inherited tolerance. We didn't publish our results."

Other studies Steele cites include apparent inheritance of drug-induced diabetes, stress-induced susceptibility to gastric ulceration, and experimentally induced thyroid disorders. None is watertight support for the somatic selection hypothesis, and several can easily be faulted. For instance, the authors of the thyroid defects in rats write, "The abnormalities in the progeny in these studies are unlike those in the fathers." They conclude, "From the data presented here it is not possible to formulate an integral analysis of the significance of these changes." Sigurd Ackerman, senior author of the paper on acquired susceptibility to gastric ulceration in rats told *Science* that although his group looked at parents and offspring, "we didn't breed further. You would have to test this before you could say anything interesting." Ackerman guesses that the effect "has nothing to do with genetics."

There are interesting and puzzling phenomena published in the literature, and no purpose is served by citing weak cases.

Steele wrote in the preface to his book, "I hope to convince you that the principles developed have wide applicability in biology and allow a resolution of a wide variety of biological enigmas which resist satisfactory explanation under the contemporary Neo-Darwinian paradigm." Mitchison speaks for many when he says he believes that this hope has not been fulfilled. "It is now clear," he says, "that this is not a phenomenon that anyone should bother themselves with, unless they are directly involved with the experiments."

Meanwhile, Steele returns to Australia convinced that English academia conspired to suppress his revolutionary ideas. He even carries the notion that, far from demonstrating an open mind on the question, the invitation to work in Medawar's laboratory was specifically for the purpose of submerging him in the homebase of the classic (now challenged) work on the subject. "In their passion to refute me, they were blinded to their own data," he claims. Brent and his colleagues' view is that "Dr. Steele's extravagant claims on behalf of our own data . . . suggest an injudicious commitment to his hypothesis."

In any case, Steele's spirits lifted when, on his way home, he visited his friend and colleague Gorczynski in Toronto. While Steele has been floundering in England, Gorczynski has been pushing on with experiments. "I started a breeding program for skin graft experiments 30 weeks ago," Gorczynski told *Science*. "The early results look very promising indeed. The controls all lost their grafts by 10 days whereas 70 percent of the experimentals still have theirs after 16 days. Some look as though they might keep the grafts for a very long time."

The final results of this experiment are due in about 6 months, shortly after the results of Brent and Simpson's final repeat attempt become available. However interesting the Toronto results may be, the acid test remains their successful repetition in a second laboratory. If the results cannot be repeated independently, then the phenomenon they represent must be said to be not generalizable and therefore not very interesting.

—ROGER LEWIN