



‘All about research’—looking back at the 1987 Cervical Cancer Inquiry

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Every year on August 5, members of the Auckland Women’s Health Council gather in the grounds of National Women’s Hospital to commemorate the anniversary of the release of the Cartwright Report and to remember the women who died as a result of the ‘unfortunate experiment’.

The Council’s newsletter pages <http://homepages.ihug.co.nz/~awhc/newslett.htm> have this to say (February 2004):

‘In more recent years we have also remembered others – in 1999 the premature babies who were part of the chest tapping physiotherapy at the hospital, and in 2000 the women of Gisborne. Last year, a wreath of yellow daffodils was placed around the statue to acknowledge the Gisborne women whose lives were lost or damaged as a result of a cervical screening programme—which did not do what it was set up to do...

‘Following the ceremony in front of the statue, the party walked around the back of the hospital to a pohutukawa tree marked by a plaque, which was laid in 1993 in memory of Dr Bill McIndoe, cytologist and colposcopist at the hospital from 1963–1983; and Dr Malcolm McLean, pathologist at the hospital from 1961–1988. The tree and plaque were placed beside a path in the hospital grounds near what used to be the Colposcopy Clinic where Dr McIndoe worked and was overlooked by Dr McLean’s Pathology Laboratory...

‘...the Inquiry itself and the subsequent Report marked the end of an era of medical paternalism and arrogance which was allowed to reign unchecked.’

My knowledge of the Auckland Women’s Health Council derives from its webpages. Apart from the fact that I live at the other end of the country, my medical academic background gives me a somewhat different perspective of the events commemorated by the Auckland Women’s Health Council.

The Cartwright report, of course, recorded the findings of the Cervical Cancer Inquiry held in 1987. Specifically this inquiry related to the circumstances surrounding an unorthodox approach to treating cervical dysplasia and carcinoma at National Women’s Hospital (NWH) in Auckland by Dr G H (Herb) Green. A professional paper (Obstet.Gynecol.1984; 64:451-458) published after Green’s retirement by NWH staff members (pathologist Malcolm [Jock] McLean, colposcopist and cytologist Bill McIndoe, and others), discussed the outcome of Green’s management of his patients. This paper was brought to the notice of Sandra Coney and Phillida Bunkle, who in 1987 published an article in *Metro* magazine entitled *An ‘Unfortunate Experiment’ at National Women’s*, which eventually led to the official inquiry chaired by Judge (later Dame) Silvia Cartwright in 1987. The official report of the Inquiry, issued in 1988, is the report to which I refer below.

A couple of years ago, I found myself discussing the Cervical Cancer Inquiry with a group of 3rd year medical students in Dunedin. At the time when the Inquiry was held, most of these students would have been 5 or 6 years old. Between 1999 and 2002, I had returned to the university (teaching pathology to 2nd and 3rd year medical students) as a retired staff member helping out temporarily during a staffing crisis.

The third year of the medical course in Dunedin has for the last few years included a session that I first encountered in the student programme as 'Integrative Day – Cartwright'. As a graduate from a different era, the 'Patient Doctor and Society' part of the course, in which this session figured, was new to me. So 'what was the Cartwright session about?' I asked my student group (because at that stage they would have known little about cervical carcinoma). 'It was all about research,' was the reply.

I thought that I knew a little about medical research. Apart from directing my own transplantation immunology research group for several years, I had been a member of a couple of the first assessing committees when peer-review assessment was instituted by the Medical Research Council (MRC) in the early 1970s, and I had later (for several years) chaired the National Scientific Committee of the Cancer Society of NZ, which at the time funded most of the country's cancer research. I also knew a bit about histopathology, one of the 'bones of contention' at the Cervical Cancer Inquiry—in fact, I had done nothing else for a period of 8 years in New Zealand and London.

Despite the extensive nature of the investigation, it had always seemed to me that parts of the *research* side of the picture were missing. I doubt whether filling the relevant scientific gaps would necessarily have made much difference to the recommendations of the Inquiry. But the missing information might have explained the apparent lack of intellectual sophistication that not only allowed the 'unfortunate experiment' to get started in the first place, but also prevented it from being terminated much earlier than it was. Conceivably, it might have tempered some of the opprobrium to which Herb Green—seemingly a bewildered old man at the time of the inquiry—was subjected. But by the same token, it would also have asked why the pathologist and colposcopist took so many years to make a point that they were probably very well placed to make much earlier.

I have taken the opportunity to look at the New Zealand medical research scene in the 1950s–1970s because, although these were very exciting years for biologists, at the same time a lot of medical research, and especially clinical research, was relatively unsophisticated and unstructured. A substantial re-appraisal of research methodology followed the introduction of formal peer-review by the Medical Research Council in the early 1970s. Scientific assessment became a very different procedure from some of the so-called review processes that had operated previously. Knowledge of the basic biological processes that underlie disease was very limited in the 1950s and 1960s, relative to the huge expansion that was to come, and this was reflected in much of the research that was carried out at that time. So the session that my students had reported as being 'all about research' concerned an event that I had always seen as thin on the scientific side. I was more inclined to interpret it as being 'all about peer review', and to an even larger extent—embarrassingly—it was 'all about some of the ignorance and intellectual naivety of a previous age'.

Terminology—In talking about cervical lesions, I'll use the simpler terminology of today's undergraduate pathology classes—ie, dysplasia for all the relevant non-

invasive lesions of the cervix, and carcinoma (or cancer) for the invasive lesions. Since the hallmark of malignancy (cancer) is invasive growth, unless I am quoting others, I'll avoid using that contradictory term carcinoma *in situ*—CIS ('a cancer lacking the hallmark of cancer'), and call it severe dysplasia instead.

Today's model of neoplastic (tumour) growth has been around since the mid 1980s. It views all the relevant cervical lesions as resulting from a series of genetic mutations, whose occurrence lacks any consistent pattern—hence the clinical variability. The mutations affect a wide assortment of genes, which in their normal (unmutated) state mostly control cell growth. Invasion supervenes when a set of mutations (the 'metastatic cascade') provides the altered cells with the biological 'know how' to travel beyond their normal confines. The early mutations, whose occurrence is reflected in the cytological features of dysplasia, increase the probability of further mutations, including the potentially lethal 'metastatic cascade'. Dysplasia can, nevertheless, persist for many years without supervision of the 'metastatic cascade'.

The above conceptual framework of neoplasia (see *Scientific American* July 2003, for a brief account) does much to explain the variable and unpredictable relation between dysplasia and invasive cancer. The model was in its very early days at the time when Herb Green retired. I mention it here because those people re-reading the report of the Inquiry may find it easier to think along these lines than to get too enmeshed in the different (and often confusing and contradictory) terminologies prevailing at the time of the Inquiry.

Medical research between 1950 and the mid-1970s

I'll start by considering the background against which this all occurred. I qualified in medicine in 1948 – three years after Herb Green, and in the same year as Malcolm (Jock) McLean. Bill McIndoe graduated shortly after this. We were all students of Sir Charles Hercus, for whom the promotion of research in the Otago Medical School was a mission. The extent to which he succeeded was summarised by Prof John Ludbrook, an Otago graduate working in Australia, in his article written on the occasion of the Medical School centenary in 1975 (*N Z Med J.* 1975;81(533):133–4). Not surprisingly in this environment, all members of staff and all aspiring academics were encouraged to become involved in research. This was fine—if you had any idea how to go about it. Most of us did not.

Research training: then and now—Today's intending medical researchers are usually enrolled for a research degree, and have mentors and official supervisors. The problems to be investigated and the students' approach to them will be approved before they start, and monitored along the way. Research trainees will learn how to test a scientific hypothesis, how to present their findings, and how to defend their conclusions in the face of possible criticism. Only a little of this sort of training was available at undergraduate level in our day, and only in the medical sciences. Not surprisingly, most students of our vintage graduated with major scientific deficiencies. How well we made good the deficiencies probably depended on how quickly we identified them. There was often an element of luck in this—it depended on our chosen fields, what we read, who were our seniors and mentors, and to some extent on chance encounters.

Human biology on the eve of the golden age—By today's standards, the general public in the 1940s and 1950s was almost unbelievably ignorant of human biology. Virtually no biological sciences were taught in secondary schools; what there was, consisted mostly of botany taught in a few girls' schools. Polite conversation was delicately non-specific about biological topics, and this vague gentility served to perpetuate the underlying ignorance. Thus, the Auckland newspapers during the war referred to 'social diseases' for what we would now call 'sexually transmitted diseases'. Needless to say, there was no sex education in schools at any level. At university in Dunedin in the 1940s, the annual lecture to 5th year medical students on contraception was crowded with students from other faculties. Among many of the general public, bowel diseases and cancer were scarcely mentionable.

Against this social background, those who were familiar with anatomy, physiology, and pathology spoke a different language from those who were not. This partly accounts for some of the medical paternalism and condescension of the time, although it hardly excuses its grosser manifestations. Of all people, the distinguished biologist JBS Haldane (described by Nobel laureate Peter Medawar as 'In some respects ... the cleverest man I ever knew') was not told by his London surgeon about the spread of his cancer—an omission that had significant effects on his subsequent plans. His sister, writer Naomi Mitchison, duly complained to the *British Medical Journal* about this (see *JBS. The Life and Work of JBS Haldane* by Ronald Clark; Oxford University Press, 1984).

Quite apart from doctors' attitudes to 'telling' or 'not telling' (which varied among my contemporaries), withholding bad news was often viewed as kindness. Margaret Forster's *Good Wives?* (Vintage, 2002) describes the measures taken in his own household in the 1960s to keep Aneurin Bevan, architect of the British National Health Service, from finding out that he was dying of cancer. Arrogance and paternalism? Sometimes, but these accusations need to be considered in the context of their day.

Experimentation and the golden age of biology—The 30 or so years after the war saw the dawn of the current golden age of biology, with DNA as its incomparable opening fanfare in 1953. On the medical scene, antibiotics and better anaesthesia opened the door to procedures that had previously seemed impossible. Thus, the postwar years were a time of unprecedented medical experimentation. A vivid account of the medical research climate then and now, and of the spectacular advances that were achieved at great cost, can be found in the obituary of Francis D. Moore, one of America's major players—perhaps *the* major player—in the surgical dramas of those times (*New Yorker*, May 5 2003). The obituary goes on to describe the complete change in his attitude in the 1970s. To some extent, this attitudinal change reflected a worldwide *zeitgeist*—triggered by revulsion at the human experimentation carried out in Hitler's Germany, and revealed at the end of the war.

But the scrutiny was not restricted to clinical experimentation—it came to extend to virtually all aspects of medical practice. I mention the Francis Moore obituary here, because the same climate change (albeit a little later in arriving) took place in New Zealand.

New Zealanders as research 'loners'—A significant, and probably increasing, proportion of today's clinical research is done by large multidisciplinary teams and

multinational collaborative programmes. The situation in New Zealand in the 1950s–1970s, and especially in clinical research, was the exact opposite. Whether they wanted to or not, medical researchers often found themselves working alone. Today's communications (eg, fax, email, internet) did not exist. Geographic isolation and the cost of overseas travel added to the isolation. Medical scientists were slightly better off than clinicians. They usually worked in university departments, and their juniors were likely to be research students. The corresponding juniors in hospitals were mainly studying for specialist college qualifications and were often not particularly interested in research. For those who have to work alone, informed argument and criticism become luxuries, when in reality they are necessities.

Collections as clinical research

Clinicians looking for research projects during the years 1950–1970 could find it hard to get started, and they often ended up working on their own. One option was to study as many examples as possible of a given disease or procedure. In the first instance, this might entail accessing the hospital records and 'taking out' all the relevant cases.

Later on, with growing clinical experience, and perhaps with a published analysis of the records, it might be possible to attain some local standing as an expert. It was easy enough to keep adding to the collection as cases became available, and to examine different aspects of the relevant topic, including the effects of different treatments. These studies were unlikely to have been designed as experiments, but were more in the nature of 'wait and see what crops up and then write it up'. A new treatment in those days would have been seen as an extension of the therapeutic armamentarium rather than as an experiment.

The publications arising from a clinical collection were, of course, retrospective analyses. They had the shortcomings that go with this approach—especially the variability of the data and the difficulty of making comparisons. These faults were not always appreciated in the 1950s and 1960s, when some substantial research reputations were built up in this way. Publications arising from large collections of cases usually conferred some local cachet on the author, and an international specialist journal carried more clout than a New Zealand journal.

Indeed, getting published in an overseas journal was sometimes equated with having 'an international reputation'. Once the writer had attained this status, referrals were likely to increase, and with any luck his (in those years it was seldom her) collection would snowball. By this stage, his opinion was seldom challenged. The main difference between the collector and his non-collecting colleagues lay in the propensity of the collector to collate his results for publication.

As far as I am concerned, Herb Green's research was an ongoing collection of clinical cases. In asking his colleagues in 1966 to refer patients, he clearly had to tell them why, so he presented the relevant staff meeting with an overview of what he proposed to do. Managing these patients was always going to entail an element of 'playing it by ear'—so it is quite conceivable that there never was a detailed experimental plan of action, of the kind that we would expect today. The proposal ostensibly related to an alternative treatment plan, and was probably seen at the time as no more than an extension to Green's therapeutic repertoire. For many doctors, trying out a new treatment that they had read about, or offering a new skill that they

had acquired while on study leave overseas, was simply part of keeping up with things. Nevertheless, the observations accumulated by a clinical collector were almost certainly destined to be collated and published as a retrospective analysis, which would ultimately, at least in a teaching hospital, find its way into the departmental annual report as research. Doctors undertaking similar procedures without publishing their findings were unlikely to get mentioned in research reports. Ostensibly, they did not do research. We would look at things differently today, but that was how it was in the 1960s.

There is nothing wrong with amassing a collection of cases. People with a special interest in a given condition will tend to do this, and will often be extremely well-informed and highly experienced practitioners. Indeed, even retrospective observational research (the clinical descriptions of SARS, for instance) can still be very useful. But for the most part, by the 1960s and 1970s, large-scale retrospective analyses had had their day *as research projects*. There were better ways of collecting and presenting data. By the early 1970s, it would have been almost impossible to submit an ongoing collection as a research proposal using the format introduced by the MRC (Medical Research Council—currently the Health Research Council).

Some scientific questions about Herb Green's research

I now consider some of the scientific aspects of Herb Green's research. The Cervical Cancer Inquiry took place in 1987 and related to clinical and histological investigations, which had had their origin a generation earlier. My familiarity with both research generations prompted me to ask four questions relating not only to the science of the period, but also to the understanding of some of the science, which I suspect to have been rather less than was assumed at the Inquiry.

Proving a hypothesis?—I am almost certain that Herb Green did not know that that a scientific hypothesis has to be falsifiable. After reading the report of the Inquiry, and also Sandra Coney's book (*The Unfortunate Experiment*; Penguin, 1988) which provides some additional transcripts from the Inquiry), I concluded that only a small minority of the *New Zealand* players in this drama (the epidemiologists) clearly indicated that they knew this. The references in the Inquiry to proving a hypothesis left me feeling very uneasy about the level of understanding of many of the other participants.

The word '*hypothesis*' is often used by all of us to mean no more than 'a sort of idea'. Strict scientific usage requires that a hypothesis be *testable* and *falsifiable*. Indeed, in contradistinction to what is widely assumed, a scientific hypothesis *cannot be proved*. At best, one can obtain evidence that is consistent with it. This information is sufficiently basic to figure in today's secondary school biology syllabus (and it certainly did not figure in secondary school science in the 1930s and 1940s). Thus, Herb Green's aim of proving that cervical dysplasia does not lead to invasive cancer should have entailed *falsifying* this contention. This should not have taken very long—whatever time it took to record the first case of invasive cancer.

I have read and re-read the relevant pages of the report of the Inquiry trying to ascertain whether Herb Green knew this. All the evidence leads me to conclude that he did not. This sort of misconception can be sorted out quite easily in an informal student class, or at a departmental seminar, but it can cause enormous difficulty in the

context of a formal inquiry, when not only is it central to the whole investigation, but when it is not officially identified as a problem.

Thus, while Prof David Skegg (*Report of the Inquiry*, pp32–33) commented on the inconsistencies in Green's approach, had his investigation been set up with the aim of disproving a hypothesis, I suggest that Green himself never knew that he was supposed to be falsifying anything. Rather, I think that he intended to accumulate a large series of cases in which dysplasia had persisted for years without malignant transformation, and in due course to record his observations retrospectively.

If I am correct, Herb Green would probably not have appreciated the points made by David Skegg at the Inquiry about falsification. Furthermore, he (and ? his chief Prof Bonham) could have been bamboozled by the discussion of whether the word 'invariably' had been used in relation to the proposal that he submitted to the medical staff in 1966. A few years later, such a misconception might have become apparent during the course of MRC scientific assessment.

Pre-cancerous conditions (of which cervical dysplasia is one of many) increase the likelihood of developing a specified type of cancer. The concept is statistical—it is a matter of probabilities. As Kolstad indicates (*Report of the Inquiry*, p23), the evidence that supports classifying a condition as pre-cancerous, is circumstantial. We do not usually expect to observe the actual transformation of the original lesion into a cancer.

Herb Green aimed to 'prove' his hypothesis by carefully observing that dysplasia did not lead to cancer—and that was how it was presented to the medical staff in 1966. Unfortunately, the proposed methodology was equally appropriate for showing that dysplasia did lead to cancer. Paradoxically, and I am sure unintentionally, he ended up demonstrating (via the paper by McIndoe et al in 1984; *Report of the Inquiry*, Appendix 7) more convincingly than had been done before, the transition of dysplasia to cancer. I do not for a moment think that any group of New Zealand doctors would ever have condoned a clinical management plan that entailed watching cancers develop. Those attending the 1966 meeting at NWH simply did not see the proposal for what it was.

If Herb Green was under a misapprehension about scientific hypotheses, I doubt whether too many of his NWH clinical colleagues were any better informed. None of the medical staff seemed to see that the whole approach to Green's hypothesis was 'back to front', as it were. A misconception like this, if it occurred, is no more than a commentary on the general state of scientific sophistication of those people at that time. Most of the clinical medical staff would, after all, have had little reason to ponder over the formal approach to a scientific hypothesis. This involves a mind-set rather different from that of routine clinical practice, and certainly different from that usually prevailing at staff meetings with multiple agenda items.

To those inclined to say 'they should have seen it for what it was!', I agree that it would have saved all sorts of trouble. Nevertheless, over 20 years later, comparable scientific shortcomings appeared to be widespread at the Cervical Cancer Inquiry. (Otherwise, why did nobody seize upon the points raised by David Skegg, and ask whether the NWH approach was an appropriate way of dealing with a scientific hypothesis?)

The medical staff, and particularly Herb Green, have been accused of all sorts of arrogance in rejecting criticism. Whatever part the personalities of all the participants in the Inquiry did, or did not, play, the lack of scientific sophistication—in my opinion the central problem—had its genesis in ignorance rather than arrogance.

There is a certain piquancy in noting that Karl Popper, the distinguished philosopher who established that a scientific hypothesis should be falsifiable, was working in Christchurch at the time when most of us were students. Physiologist Prof J C Eccles (a future Nobel laureate) invited him to Dunedin to speak in his department.

Making predictions from hypotheses—Also apropos of scientific hypotheses, I wondered whether anybody at NWH in the 1960s and 1970s realised that a scientific hypothesis should *generate predictions*? Herb Green had hypothesised that severe dysplasia was a different disease entity from invasive cancer.

If this were so, it could have been predicted not only that:

- (a) Severe dysplasia could occur on its own (which was already known), but also that
- (b) Invasive carcinoma could occur on its own, ie in the absence of associated severe dysplasia.

Therefore, I wondered whether Herb Green's hypothesis might not have been approached from the 'other end of the disease spectrum' by attempting to falsify prediction (b) above?

Herb Green is said to have regularly disparaged the specialist opinion of histopathologist Jock McLean. Most pathologists subjected to this sort of thing would have been hopping mad. But viewed from afar, it is pertinent to ask whether Herb Green might have done this simply because he belonged to that group of aggressive players who rather enjoy 'trading intellectual punches'? Might it have been possible to beat an aggressive Herb Green at his own game? I think so.

The falsification of the prediction that cancer could occur on its own without severe dysplasia would have dealt a mortal blow to Green's hypothesis. A purely histopathological investigation into which no clinical input was required, need not have involved Herb Green at all, so the exercise could have been free of verbal punch-ups. As long as the hospital had retained its hysterectomy specimens (and most hospitals would have done so in those days), it should not have taken too long to answer the question: *How frequently is unequivocal invasive cancer accompanied by severe dysplasia in the adjacent cervical epithelium?*

The two pathological lesions were already known to be associated—indeed, Jock McLean himself referred to NWH material showing the association (*Report of the Inquiry*, p76). More information was needed from the NWH cases on *how often* dysplasia accompanied cervical cancer. The existing literature already hinted at a figure not too far from 100% (references cited in the 2nd edition of R A Willis's *Pathology of Tumours* (Butterworth, 1953—the virtual bible on neoplasia in its day). The demonstration that invasive cancer did not occur in the absence of severe dysplasia of the adjacent epithelium could have provided compelling evidence that the two lesions were related.

Such an investigation should not have been too difficult to carry out. With any luck, most of the relevant information would have been available on existing slides without

calling for the preparation of more sections. Even at the slow rate of one specimen examined in detail each day, it would not have taken long to accumulate results from, say, 50 consecutive cases of cervical cancer. The findings would almost certainly have been publishable in a peer-reviewed international pathology journal. With suitable high-quality photomicrographs to illustrate the basis of the diagnoses, the conclusions would have been open to scrutiny by all, and could have supplied a reference point against which future discussions of this contentious project were considered. Once the information had been published, it would have been irrelevant whether Herb Green believed the results.

So why was it not done? I don't know, but my guess is that (like Herb Green) Bill McIndoe and Jock McLean had not given much serious thought to scientific hypotheses. It was a missed opportunity, but it could hardly be called anybody's fault.

A Eureka experience?—My next question concerns the origin of the hypothesis which Herb Green set out to prove, and to which he adhered so tenaciously. I was looking for the sort of information that in later years would have appeared in the Justification section of a standard research grant application—a detailed account of the evidence that led him to believe that some of the histological changes interpreted by most pathologists as being sinister were, in fact, innocuous. Epithelial dysplasia elsewhere in the body (mouth, skin, colon, for instance) has for a long time been regarded as pre-cancerous, although in some situations, many years can elapse before a cancer develops. Indeed, it may never do so. Green had, of course, already had a patient with a high-grade smear who had refused treatment, and who had nevertheless survived for many years in good health. He was no doubt acquainted with the slow progression rate of some other dysplastic lesions. A comparable behaviour pattern of cervical dysplastic lesions might offer a potential rationale for avoiding hysterectomies.

Green's postulate that cervical dysplasia was relatively innocuous was, of course, ultimately going to require an answer to the question: '*If it is not a pre-cancerous lesion, what is it?*' I suggest that Green had a pretty good idea of what the lesion was, but that his interpretation was wrong. He knew that histological sections of the foetal cervix often showed lesions very similar to adult cervical dysplasia and cancer. Thus, he argued that dysplasia in the adult might represent *persistence of a foetal structure*. And because the foetal lesion clearly did not lead to cervical cancer in childhood or adolescence, he deduced that the adult lesion was therefore less dangerous than conventional gynaecological wisdom deemed it to be. This interpretation accords with several pieces of evidence from the inquiry:

Paragraph 1 on p34 of the Report quotes Herb Green as saying,

‘Around about 1963 I thought of the possibility that abnormal cytology in women later developing CIS (= carcinoma *in situ* or severe dysplasia) or cancer may have been present at birth: this was because many pathologists and clinicians whom I consulted, diagnosed dysplasia or CIS in autopsy specimens of cervixes of stillborn infants’

It was an unusual idea, which should have provoked all sorts of discussion about the validity of the interpretation. It called for a contribution from histopathologists who had had experience with foetal and neonatal tissues, and possibly also from a developmental biologist. Unfortunately, New Zealand had not too many of these

people at the time. Thus, I was curious about the identity of the ‘many pathologists and clinicians’ said to have made the diagnosis. Not many autopsies are normally carried out on stillborn babies. Nor are many histopathologists very interested in examining the foetal cervix. Anyway, whatever Herb Green had seen in the tissue sections no doubt prompted him in 1963 to start looking for the corresponding ‘abnormal cells’ in vaginal smears from newborns. No abnormal cells were found in the smears. The intellectual isolation of the day meant that (as far as I can tell) nobody asked the important question ‘*Why not?*’ It might have led to a more critical appraisal of the tissue sections.

If the neonatal smears were uninformative, the evidence from the tissue sections remained important. At least two patients in the 1966 series (*Report of the Inquiry*, p33) were told about it:

Patient code 4F1: ‘He (Dr Green) told me that there was 9 out of 10 women have cancer and he said that in my case, if I went to my normal GP they would panic.... They would be rushing me into hospital.... and he says in cases like that, it does lie dormant.... ‘

Patient code 4S: ‘Every person is normally born with cancer, but it is the type of cancer that is dormant....He said sometimes it just flares up every now and then.....’

Although patients’ recollections are prone to inaccuracy, I doubt if two people could independently have come up with the same very unusual story that ‘we all have cancer but it lies dormant’, had they not actually heard something very like it.

As late as 1979, Herb Green noted (in *N Z Med J.* 1979;89(629):89–91):

‘Some observations (unpublished) by the present author on the histological features of the cervical epithelium of infants dying at or around term have shown appearances which some pathologists (without knowing the source of the material) have been prepared to describe as at least dysplastic if not neoplastic’.

Oddly, and tantalisingly, Herb Green did not publish any representative photomicrographs. Inexplicably in the circumstances, nor did anybody else at NWH seem to make a point by referring to photomicrographs. Yet they were at the time easily obtainable. So we are left guessing what Herb Green had seen in the foetal cervix. I suggest that he almost certainly saw the early phases of *squamous metaplasia*— a benign but actively developing lesion, occurring at a time when the foetal cervix was already engaged in the normal growth spurt that occurs before birth.

The process is described in some detail in Yao S Fu’s *Pathology of the Uterine Cervix, Vagina and Vulva 2nd edition* (Saunders, 2002). Metaplasia involves the conversion of one type of epithelium into another and is fairly common in the cervix from late foetal life to the 8th decade. While Herb Green was no doubt very familiar with its *adult* manifestation, in which the mature squamous cells are easy to recognise, the immature cells in the early stages of the foetal lesion are a more difficult diagnostic problem. Indeed, as Yao Fu points out (Figs 2-22 and 2-23) the appearances *superficially* resemble the lesions seen in adult cervical dysplasia, or even invasive cancer, for which they can be mistaken.

Thus, I suggest that Herb Green's 'dormant cancer' idea stemmed from his failure to realise that metaplasia in the foetus was a different lesion from adult cervical dysplasia. From his 1979 comment (above), it appears that he was not alone in thinking this. Yao Fu's photomicrographs, incidentally, probably explain why Green failed to identify 'abnormal' cells in vaginal smears from neonates – the relevant cells were deeply situated, and would not have been detached during the preparation of the smears.

It is easy enough to be disdainful of this whole idea today, especially with the advantage of being able to view things within the conceptual framework of the current model of neoplastic growth (which has dysplasia a few mutations away from cancer). This was not possible in the 1960s, when Green's ideas would have looked considerably less 'way out' than they do today. Nothing highlights the downside of intellectual isolation more tellingly than this story. Indeed, his hypothesis should have brought the devil's advocates out of their laboratories.

Instead, apart from some unidentified pathologists, who did not know the source of the material (referred to in his 1979 publication), the only record of any communication seems to have been with a couple of patients. Anybody who has worked in isolation will know how easy it is to become devoted to a misconception, especially if it has involved something of a Eureka experience—one of those 'highs' that reward researchers for having what at the time seems to be a great idea.

Notwithstanding the intellectual isolation in which Herb Green worked, it remains a mystery to me why none of his colleagues were acquainted with the 'dormant cancer' idea.

Was it because he was better informed than his colleagues on cervical histopathology, so did not bother to discuss it with them?

- Because he told them about it, but they were not very interested, or it did not register with them?
- Because nobody ever asked him what evidence had prompted the 1966 hypothesis (by then his 1963 neonatal vaginal smear project had probably been forgotten)?
- Because he did not want to be asked why the 'abnormal cells' present in the foetal cervical tissue sections did not show up in the newborn vaginal smears?
- Because he suspected that GPs, as well as his own colleagues, might have panicked when they heard the "dormant cancer" idea?

Maybe there is a grain of truth in all these possible explanations.

Scientific peer review: then and now—The inquiry raised the subject of inadequate peer review on several occasions but was vague not only about the *process*, but more importantly about who should be doing the reviewing and when. The expectation that Herb Green's clinical colleagues had the know-how to evaluate some *scientific* aspects of his contentious investigation was, I think, unrealistic. Scientific assessment underwent a radical change in New Zealand during the early 1970s. For all practical purposes, New Zealand adopted international practice. Something very different had obtained before this.

The apparent lack of understanding of the process of scientific peer review, and what it entailed over the relevant period, was a gap in the Inquiry as far as I was concerned.

To provide a standard against which to consider the so-called assessment carried out in 1966, it is useful to outline the process set up by the Medical Research Council in the early 1970s. This represented the country's first attempt at *systematic* scientific review. Research proposals were submitted in a standard format that basically asked what was being done, why it was being done, how it was to be done, what staff were involved, whether their qualifications were appropriate, what benefits were likely to accrue from the study, how long it was likely to take, what it was going to cost, and so on. Furthermore, a proposal was typically supported by up-to-date references from the relevant literature.

All the MRC committee members were experienced researchers. A research proposal was first considered by two committee members who provided preliminary written reports. In the general discussion that followed, all the other committee members commented individually, and the opinions of national and/or international referees were made available. A numerical score, using the designated MRC scale, was finally assigned privately by each member. Neither the applicant for a grant, nor any of his/her associates, was ever present in the room while the proposal was being discussed.

Within the limits of what is possible in a small country, the members of the four committees were selected for their knowledge of a given field. Thus, a molecular biologist would not usually be a member of the clinical committee, and vice versa. Reviewing a grant application could be time-consuming if it called for 'nitpicking' checking of data or journal references, or if it entailed writing a balanced report on a contentious application. Formal assessment of this type is simply not the business of the usual medical staff meeting.

Research funding organisations such as Cancer Society, National Heart Foundation, Neurological Foundation, Arthritis Foundation, and so on, subsequently adopted the MRC format. Most of the funding for university and hospital biomedical research has (for many years) come from the above sources—so for the last 25–30 years, it has been almost impossible to gain a significant research grant without submitting an application along these lines.

In a recent (2003) personal communication, Jim Hodge (formerly Director of the MRC) who instituted this assessment process, commented:

'In retrospect, I think the most important thing that I did during my time with the MRC was to persuade (? force) the council to adopt a proper peer review system. The members had naively assumed that appointing a professional as Chief Executive Officer would solve all their problems of assessment of research quality; and it took some time and effort to persuade them otherwise.'

It was a hugely important move and changed New Zealand medical research irrevocably for the better.

Scientific peer review pre-1970s—Prior to the institution of individual project grants, the MRC used to provide block grants to academic departments, the disbursement of which was the responsibility of the departmental head. Such peer

review as there was at the time, took place at departmental seminars or institutional research meetings, at national and international meetings, and finally when the work was published.

For an individual researcher, the extent of the peer review was apt to be variable, and depended on the culture of the department or institution. Medical sciences departments were more likely than clinical departments to hold regular research meetings, and junior scientists were usually more likely than junior clinicians to argue with their seniors.

When individual project grant applications replaced most of the departmental block grants in the early 1970s, preparing a formal application turned out to be a much more demanding task than contributing a section of the departmental annual report, which had until then constituted the main communication with the MRC for those of us who were not departmental heads. The informed national and international criticism to which most of us were now to be individually subjected (via our grant applications) no doubt sharpened our intellectual faculties more effectively than almost any other relatively simple administrative change could have done.

Herb Green and the Medical Research Council?—It seems almost certain that Herb Green's research was never submitted for assessment by the MRC. Amassing a collection of cases costs nothing, so there is no need to apply for financial support. The former Director of the MRC (Jim Hodge) and Deputy Director (Colin Geary) have both confirmed that Green never held an individual project grant from the MRC (personal communications 2003). His work had started in the days when funding was via departmental block grants, and Green did figure as an associated investigator, and later as a principal investigator, in some of the annual reports to the MRC provided by Prof Bonham.

All departmental research activity was apt to find its way into the annual reports, irrespective of whether it had used MRC funds. Although Herb Green's research was said to have been ongoing, his name appeared in some annual reports but not in others. Indeed, in the personal communications (2003) referred to above, neither Jim Hodge nor Colin Geary is certain why the Inquiry (p64) reported that Herb Green's research was assessed by the MRC in 1982. Since he did not hold a grant, the MRC would have had no reason to assess his work.

Our theories may be wrong but our data must be right—Some of the data relating to the Cervical Cancer Inquiry leave me feeling uneasy—at least from this distance. For at least some of the time period covered by the investigation, it appears that for a number of patients, two different histological diagnoses (McLean, Green) had been made on the basis of the same cervical lesion. The in-house investigation undertaken at NWH in 1975 had its origin in a conflict about these histological diagnoses. So who made the definitive diagnosis? When? Which diagnosis is in the hospital records? When did it get there? And which one appeared in those hospital records that were examined in 1975 by the in-house investigating committee (Drs Macfarlane, Faris and Seddon)?

Since the inquiry recorded that the in-house committee of investigation had no terms of reference, what did its members know about the histological disagreement and the memos relating to it? Did the differences of pathological opinion involve only dithering on the basement membrane—ie, the decision on whether there was micro-

invasion. (This is a comparable problem to the harder 'run out' decisions by the 3rd umpire in cricket. It concerns difficult borderline situations open to differences of opinion.) Or did it involve major diagnostic disagreements?

The absence of photomicrographs in a couple of situations that seemed to be calling out for them is strange. For histopathologists, they exemplify the aphorism that one picture is worth 1000 words. One photomicrograph with an arrow pointing to the lesion of interest, and accompanied by the caption: 'The arrow marks the lesion interpreted by A as ... and by B as ...' would have been more effective than a dossier of memos. Photomicrographs were easy enough to obtain in the 1960s and 1970s, so why did nobody bother?

Maybe it is possible to resolve the data about which I feel uneasy into a set of clear unequivocal results. But that calls for better access to the data than I have.

For my former student group—the salient points

My students are supposed to leave class armed with the salient points of the topic under discussion. So the scientific pieces that were missing from their 'all about research' session go something like this:

- Herb Green's 1966 project exemplified the relatively unsophisticated approach to clinical research of many of his vintage of medical graduates. He almost certainly had a major misconception about scientific hypotheses. Had comparable ignorance not been widespread among his professional colleagues, the investigation could have been concluded quite quickly (in months?).
- The investigation was basically a collection of clinical cases whose attributes were to be reported retrospectively. The 1966 proposal was a request for more referrals to try a new treatment. He explained why he wanted the referrals—but this was not a formal project application as we write them today.
- New Zealand had no formal system for scientific peer review of research proposals before the early 1970s. This was a defect of the age. Even if such a system had existed, the hospital staff were not qualified to evaluate some of the scientific issues raised by Herb Green's hypothesis. And scientific peer review (as opposed to ethical review) is usually a function of one or other of the research funding organisations.
- The conservative treatment of cervical lesions was prompted partly by the known long duration of some pre-cancerous lesions, but also by his misinterpretation of cervical histology from stillborn babies. This misconception was not helped by the relative isolation in which Green worked. Strangely, his clinical colleagues were almost certainly unaware of the evidence underpinning Green's conservative treatment. It was never published in a way that could be properly evaluated. Today's standard model of neoplastic growth had not at the time been developed.
- It costs nothing to collect clinical cases, so there was no need for a research grant. The work thereby escaped a good deal of early scrutiny. Green never held an individual MRC project grant and his work was never assessed by the Council. He featured in some of the annual reports of the MRC because the head of his department held a block grant from the Council, which called for an annual report.

All departmental research activities were apt to figure in these reports, irrespective of whether they used MRC funding.

- To those who ask if scientific naivety and ignorance is a bad thing—of course it is. But the scientific glass-house in which we all live has walls as thin as the cover slip on a histology slide, so throwing stones is not particularly useful. However knowledgeable we might seem today, we are all doomed to be overtaken in our own fields tomorrow. It is easy enough to see Herb Green as the fall guy for his era of clinical research.
- In failing to take into account some important changes that had taken place between the 1960s and 1980s, the Inquiry missed identifying the scientific problems that were central to the whole affair.

Some more trees

Coming back to the tree at National Women's Hospital: Trees are lovely things—we should plant more of them. I'd plant one to remind an institution that suffered as a result of the inquiry, that it has hosted some of the country's top biomedical scientists.

Indeed, I'd add another tree to thank all the staff—yesterday's and today's—for caring for thousands of patients over the years. Hospitals are safer places when they retain some *esprit de corps*, and when the staff can feel that their work is appreciated.

And please, a tree to remind everybody that Jim Hodge instituted the sort of peer-review assessment that halted inferior investigations before they got off the ground—a system that all the larger research funding organisations in the country duly copied a few years later. I am keen on this tree because many people in this country give generously to medical research. I would hate them to think that we are not deadly serious about what we do with their money. Also apropos of scientific peer-review assessment, another tree would acknowledge the overseas experts who review this country's grant applications. They work behind the scenes and give of their time and expertise for nothing.

Somewhere in this grove I'd like to record two comments on research. Specifically, and in relation to medicine, clinical research is undertaken simply because the current diagnosis and/or treatment are not good enough. In a more general sense, we should carve the message into stone that it was research—finding out—that brought our ancestors out of caves.

A final question

We teach our pathology students that in biology, as elsewhere, 'there is no such thing as a free lunch'. Thus, an account of a vitally important process like inflammation always comes with the questions: What harm does it do, and what does it cost? Turning to the Cervical Cancer Inquiry, undoubtedly it righted some wrongs. But what harm did it do, and what did it cost? Perhaps 16 years is long enough after the event for somebody (who knows more than I do about the current O&G scene) to scan the balance sheet dispassionately.

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Acknowledgment: This account of medical research in the third quarter of the last century owes much to discussion and correspondence with my contemporaries. As might be expected, their research experience has varied. Some have been academics, and this group includes distinguished international endocrinologist Mont Liggins. Many others have belonged to a group that I'll call inadvertent researchers—clinicians who introduced new treatments in their day, only to find a later generation classing their way of doing things as research. I hope that they will agree that this was how it was.

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Reference:

The Report of the Committee of Inquiry into Allegations Concerning the Treatment of Cervical Cancer at National Women's Hospital. Report. Auckland; 1988. Available online: URL: <http://www.womens-health.org.nz/cartwright/cartwright.htm> Accessed August 2004.