The man behind the margins

Peter McIntyre

Roland Holland started investigating mammograms and their relation to pathological findings as part of the first European pilot of breast screening. His findings were later used by Umberto Veronesi as key evidence in support of breast-conserving surgery. More than 20 years on, his data are again being called into service, this time by America's brachytherapists.

Roland Holland started a new life at the age of 40 as a paediatric pathologist in Nijmegen, the Netherlands, after escaping with his family from Hungary, via Nigeria, sort of disguised as a Dutch airline pilot.

It was 1976, and although he was not immediately aware of it, Nijmegen and Utrecht had just become the second region in the world to set up a pilot mammographic breast screening programme.

Sooner or later, this inquisitive pathologist was bound to start poking his nose into the pilot programme, and this led to a confrontation in the corridor with one of the young radiologists pioneering mammography reading. They settled their differences to strike up a lifelong friendship and teamwork that helped make the Dutch screening programme the most respected in Europe.

Holland's work on the clustering of tumour foci in the breast was used by Umberto Veronesi in Milan and by others to develop procedures for breast-conserving surgery. Today this 1985 paper is making renewed ripples, as radiotherapists consider how to narrow the range of radiotherapy dosage after surgery.

Before getting into the science, or even the adventure story, we have to deal with this coincidence of name between person and the country, that we shall call the Netherlands. Did he change his name from something more obviously Hungarian, or choose the country because of his name? In fact, neither is the case. The name Holland goes back a long way in Hungary, apparently.

"My Dutch friends say: 'Your ancestors were probably slaves on our ships, and they did a good job so we gave them the name Holland,'" he says.

He has certainly done a good job for his adopted country and some might say he is still shackled to his work at Nijmegen, even after his formal 'retirement', but it does not seem likely that Holland would have made a good slave. He would probably have escaped.

Holland did his medical training in Budapest, specialising in pathology, because his (doctor) father advised him that this was the foundation of good medicine. He took part in

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the Hungarian uprising of 1956 as a student. "Half of us got a gun and the other half who had a bicycle were messengers. I was in the bicycle group. Afterwards, I was not in direct danger, because I had no gun. I wanted to escape but my father and family were very depressed about that and asked me not to."

As an out of favour non-Communist Party member, his career was blighted. By the early 1970s, he was married, with a young daughter, and deputy head of pathology at Peterffy Hospital, Budapest.

He wanted out. In 1973, Hungary was recruiting a pathologist to complete a Hungarian medical aid team in Nigeria. The rest of the team were trusted Party members. Holland, and his family, were included because none of the Party pathologists agreed to go.

"This was a wonderful opportunity. We spent three years in Nigeria. My duty was to set up and run the first pathology laboratory in Port Harcourt (the coastal 'Garden City'). My greatest reward was that when I left, the surgeons said we can never work without a pathologist again."

Under the terms of his contract, someone arrived regularly from the Hungarian Embassy to take away half of his salary. To make up the shortfall, the whole Hungarian team worked in private practice. Holland became company doctor to a number of large international companies and their staff, despite warning them that as a pathologist "I am only really an expert after you have already died." Studying at night he taught himself to be a family doctor.

Senior staff at the Dutch multinational Interbeton heard that he was thinking of trying to gain admittance to the US, and urged him to try the Netherlands instead. When he was sent on a two-week course to England, his contacts arranged for him to visit Nijmegen on the way.

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"Holland's job was to compare the biopsy specimen with the microcalcifications on the mammogram"

The Professor of Pathology Peter Vooijs promised him a job, once he had completed his tour in Nigeria.

There were troubled sounds out of the Dutch Embassy in Lagos, but Holland was backed by powerful friends in industry who ensured that the Hungarian Embassy heard no hint of his departure. A Dutch-American helicopter company flew him to Lagos and walked him around the back of immigration control wearing a Dutch pilot's tie.

There he joined his family on a KLM flight for Amsterdam. "They sent a note from the plane, to my Dutch friends saying 'your doctor is safe'. I am still very emotional when I think about this."

Holland arrived at the University Medical Centre at Radboud University in 1976 as pathologist for the new paediatric oncology centre. Aged 40 he was both student and expert, travelling to the Netherlands Cancer Institute in Amsterdam every weekend to study paediatric cases, and working in Nijmegen during the week, while at the same time learning Dutch.

What he found most enjoyable was being included in ward visits to see the children – and the fantastic cure rate. "I loved this job and we were very effective with children. This was 30 years ago and this was my first encounter with a multidisciplinary approach. It was an innovation here; you saw the patient first and later examined the specimen."

Even a University Centre like Nijmegen did not see enough child cancer cases to keep a hard-working pathologist busy, and Holland began also to work in general surgery, examining breast cancers uncovered during screening.

Inspired by the New York breast screening programme, William Penn, head of the Radiology Department, set up the Nijmegen pilot to test the potential for national screening in the Netherlands.

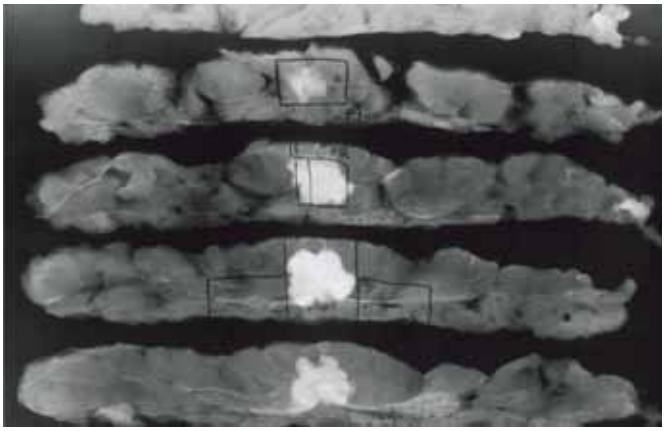
X-RAYS AND BIOPSIES

Many of Holland's studies deal with the detection of the precursor lesion of breast cancers, so-called ductal carcinoma in situ (DCIS). Mammography does not detect DCIS directly, but detects the microcalcification that occurs as a cancer progresses. Holland's job was to compare the biopsy specimen with the suspicious microcalcifications on the mammogram. In one of his first examinations he reported that there was no calcification in a biopsy taken on the strength of a radiologist's report. The young radiologist, Jan Hendriks, came to visit this junior 'idiot' who was questioning his expertise. They met in the corridor and after a healthy exchange of views, decided that they liked what they saw and that it was probably the surgeon's fault for sending the wrong bit for testing.

Holland, Hendriks and a young radiographer Henny Rijken started working together to understand the relationship between the mammogram and the pathological findings, learning about each other's jobs on the way. Holland became personally skilled at reading the mammograms, while Jan Hendriks and Henny Rijken became familiar with the pathology of breast tumours. "They called us the troika. We did courses, scientific projects and publications together. We came back here at 9 o'clock in the evening and worked two to three hours without anyone disturbing us. We never called what we did work."

After the screening programme had been running for its first four-year cycle, it became apparent that screening was not finding all the cancers. "I was starting to work on this. I saw the so-called 'missed' interval cancers. They were categorised as negative from the mammogram, and women come back with a palpable mass. This was disappointing."

Holland produced the first international paper on interval cancers in the 1980s, and in



Hidden tumours. By comparing breast cancer biopsy sections against their corresponding X-ray images, Holland and his team were able to show that tumour foci did not always have microcalcifications, which explained why some cancers were not being picked up at mammography screening

1984 defended his thesis on "New aspects and pitfalls in the diagnosis of breast cancer" 'cum laude'. "Invasive cancers start always as in situ intraductal (DCIS) or intra-lobular (LCIS). At a certain point they break through the basement membrane and they become invasive, forming a tumour mass.

"So long as they are in the ducts or lobules, limited to the basement membrane, there is no possibility of spreading to the lymph nodes or to other parts of the breast. They are theoretically 100% curable if you take them out. If it is already invasive, then you have always a certain percentage chance that it has already spread when detected.

"If we could find all breast cancers in their in situ intraductal phase, nobody would die of the disease. Unfortunately, not all intraductal cancers have microcalcifications. In others the process of becoming invasive is rapid and the two-year screening interval is most likely too long."

In almost two-thirds of invasive cancers, there are multiple foci in the breast, even if they do not show up on the screening mammogram.

Holland did a study with the Joint Centre of Radiotherapy at Harvard together with Jay Harris, Jim Connolly and Stu Schnitt. "We showed that if you have a recurrence of cancer after breast-conserving therapy it is usually based on residual intraductal foci. If you leave this behind, even if you irradiate the breast, the intraductal tumour will grow out and recur.

"The question was: How far do these other foci exist around the detected lump? That was the study that nobody had done. If you take out a lump and irradiate the breast you don't know any more what you have left behind. You could only do that on mastectomy specimens."

Margins of safety

That is what Holland set out to do, slicing and examining 314 breasts that had been removed by mastectomy, but could have been candidates for breast-conserving surgery. Of these, 282 breasts had invasive cancers, and of these, only 105 (37%) did not show other foci. By measuring the distance from the 'reference' tumour, Holland estimated what percentage of tumours would be left behind after each extra centimetre of breast was excised.

Holland, Hendriks and two colleagues (Veling and Mravunac), calculated that if invasive cancers that were 4 cm or less were removed along with 3–4 cm of surrounding tissue, invasive cancer would be left behind in 7%–9% of women, with non-invasive cancer left behind in a further 4%–9%.

Their paper was published in *Cancer* in September 1985. Holland says he had no idea of the significance of this work until it was finished. "The world discovered it after three or four years when they started doing breast-conserving surgery."

Veronesi in Milan pioneered the route from

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mastectomy to breast conservation. He argued that if the cancer had already spread, mastectomy would not help, while if it had not spread, taking the whole breast was unnecessary. Why not just take the tumour? Holland's work was just what he needed to support his practice.

"In my studies in Nijmegen, working with many hundreds of mastectomy specimens, I came always to the same answer – a 5% chance that there was a tumour in a remote quadrant, other than the one where the primary tumour was found. Veronesi put my figures on the wall of the operating theatre and said, 'Look, he says we have to excise this area.'"

Holland's work was based on the morphology of the tumour. A few years later, clinical statistics began to tell the same story. Just as Holland predicted, there was a 90%–95% chance that any recurrence appears in the same area of the breast and not in a remote quadrant.

Research over the past 20 years has revealed a more complex picture, without shaking the underlying arithmetic. In 1996 a study by JS Vaidya and others at the Tata Memorial Hospital in Bombay used three-dimensional techniques to visualise the breast. They came to a different answer – finding remote multicentric foci in 15 out of 19 breasts. However, studies continue to show that more than 90% of early recurrence is in the same quadrant as the primary tumour.

The key question is why some foci of DCIS develop into invasive cancers, while others do not. Holland believes that the answer lies in the differentiation of the cells. "Poorly differentiated cancer with many mitoses can go crazy in a short time and in one to one-and-a-half years become an invasive cancer. A well-differentiated tumour is quiet, the nuclei are evenly distributed and approximately the same size. It may become invasive in 10 to 15 years. Maybe these foci are biologically less important, but we never see a DCIS disappear."

Holland was recently approached by radiotherapists at the Annual Congress of the American Brachytherapy Society, who dusted off his 1985 paper and asked him to revisit his figures applying current criteria about tumour size and type, the extent of microcalcification and the age of the patient. They hope to use the results to guide them in reducing the area of the breast they need to irradiate. Holland has promised to help them to estimate a 'safe zone'.

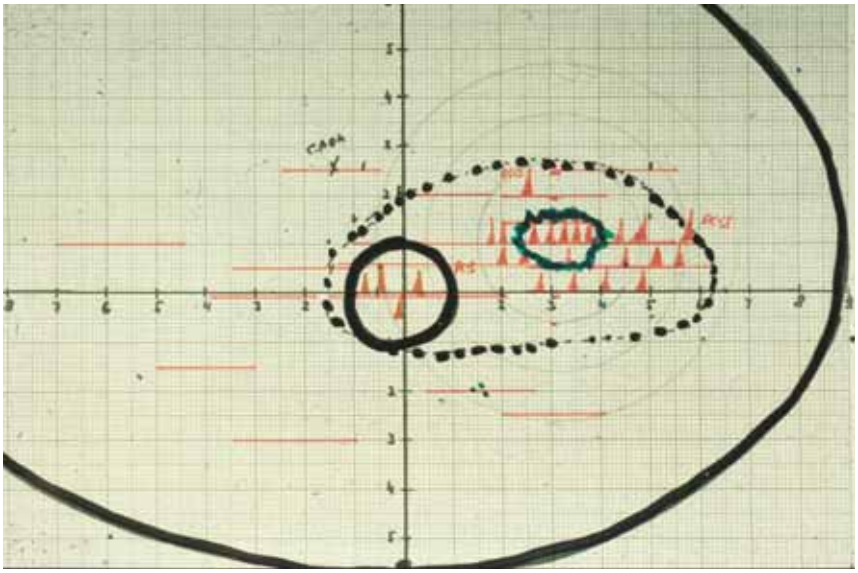
In 1989, on the basis of the mortality decrease shown in Nijmegen and Utrecht, the Netherlands approved a national breast screening programme for women aged 50–69, at two-year intervals, although it took until 1996 to extend this to the whole country. In 1998 the upper age band was increased to 75.

Mammography is done by radiographer technicians in 68 mobile buses, who send the mammograms to 28 radiology reading centres in the nine screening regions of the country.

In 1988 Holland was appointed director of the National Expert and Training Centre for Breast Cancer Screening (LRCB) at Radboud University Hospital, responsible for training and for quality assurance of the nation-wide population-based screening project. Every radiographer and radiologist in the country must train here before being allowed to work in the national screening programme.

For many years the Netherlands had the lowest referral rate of any screening programme in the world – until 1999 it was under 1%. One of the last papers that Holland and Hendriks worked on together with the support of epidemiologists in Nijmegen and Rotterdam – Hendriks died from melanoma in 2004 – was to look at the likely extent of missed cancers and calculate how many more would be detected if the referral rate increased.

Holland felt that the low referral rate was connected with the Netherlands being the



Surgical margins. Original drawing showing tumour distribution in a mastectomy specimen with the nipple in the centre, the invasive tumour in the upper outer quadrant and the DCIS foci surrounding the invasive tumour (triangles). The circles imitate various sizes of surgical excision, showing the amount of potential residual DCIS

European pioneer of mammography. "At that time there were no pre-operative minimally invasive procedures like core biopsies or vacuum-assisted biopsy. We were afraid that if we sent too many women for unnecessary examination and surgical biopsies they would not come back. They would say 'they operated on me when there was nothing wrong'."

As some of the cancers have only less obvious, subtle signs on the mammogram and only 20 to 30 mammograms of 1000 may show a suspicious sign, of which 5 to 6 are cancers, there is always the possibility of missing something. For this reason, each mammogram is read by two radiologists. If they do not concur, they talk to each other and come to a consensus.

Holland and his team visited the screening centres and urged them to change their practice. "I feel that the most logical thing is not to talk to each other, because consensus usually lowers the recall rate. If one of you feels she should be recalled, then recall her."

Quality control

By 2002, the recall rate had risen from below 1% to 1.3%, and is now around 1.4%. Above 3%, says Holland, there is a law of heavily diminishing returns.

As part of quality control, a team from LRCB visits each mammography reading centre every three years. They review data on the number, size and tumour stage of cancers detected. They also review the cases of 120 women who had interval cancers that had not been detected by screening. "We look at the previous mammograms and assess whether the cancer could have been detected early. Many interval cancers are very fast growing so you don't see anything on the previous screening mammograms. In some cases there is a minimal sign. And some you just miss," says Holland bluntly.

A weakness in the Dutch system is that once the recall has been issued, the national screening programme loses control of the subsequent assessment. The woman's doctor sends her to any one of 100 or more general hospitals in the Netherlands, where mammography is repeated with extra views, magnification and ultrasound if necessary. In about 20% of cases, they decide there is nothing wrong. The other 80% of woman are referred for histological examination.

Holland says this was a mistake – again a result of being early in the field – that they are now trying to correct. "There is not enough contact between a radiological department of a hospital and the screening radiologists, and the radiologists at the radiologist department are not trained here. Assessment must be incorporated in the screening process.

"In every visit we do, there are two or three cases where the screening radiologist had said it was suspicious, the radiologist in the hospital said it was nothing and the cancer came in half a year or one-and-a-half years. That is what we call doctor's delay. We are happy to know that EUSOMA [the European Society of Mastology] and EUREF [the European Reference

"There is not enough contact between radiology departments of hospitals and screening radiologists"

Organisation for Quality Assured Breast Screening and Diagnostic Services] are urging countries to form specialist breast centres. We are trying to change now. We could have 20 to 30 breast centres in the Netherlands with good cooperation with the screening."

When Holland planned to make his journey to the Netherlands 30 years ago, his Dutch business contacts in Port Harcourt told him he would be fine there so long as he learned to drink Dutch gin (jenever) and smoke Dutch cigars. As a cancer specialist he could not accept this definition of Dutchness. However, when he was appointed Professor of Pathology at St Radboud in 1998 he reached for another Dutch tradition to draw a lesson for screening.

"The Dutch herring is very delicious and there is always a test for the quality of the Dutch herring in May each year when the first catch of new herring start to be sold in the fish shops. I say if we can have quality control for the Dutch herring, why can't we have a comparative quality control of the management of breast cancer patients in our hospitals?"

With an award from the Queen of the Netherlands and a professorship, Holland is well accepted by the country whose name he bears. Despite being retired – radiologist Dr G den Heeten has now taken over as director of the LRCB – he works almost every day and is in demand on scientific groups and at international conferences. He also keeps a friendly eye on the progress of the breast screening programme in Hungary, where he is, today, welcomed.

He promotes multidisciplinary working where specialists tread over boundaries. "I teach people the relationship between what you see on the mammogram and the histology. I always tell radiologists to find a pathologist who is interested, and to look at everything together. Look at the mammogram and then look in the microscope."

The future of breast screening is digital. Ultimately, computers will help to highlight changes in consecutive scans for the specialist to review. "Tomosynthesis, a kind of CT scanning, can section the breast into hundreds and thousands of sections and then you will have a much better three dimensional image. You can manipulate the image and probably have a better chance of finding cancers in dense breasts of women under 50 years of age. Whether you can also reduce the number of missed cancers, we don't have yet data on that."

And that is the key question.

"Usually in medicine we tolerate 5% errors, whether it is a false-negative rate of sentinel node technique, recurrence after breast-conserving treatment, or whatever. But you cannot tolerate 25% or 30% errors. I don't think mammography will survive more than 15 or 20 years. A method must come that can detect at least 95% of breast cancers.

"I always say we are working with statistics and science, but statistics cannot tell you anything about an individual patient. We must give women the best information and tell them that we find 70%–75% of cancers, not all of them. You should not absolutely rely on screening but still palpate your breast between screening examinations."

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