

Nicholas Pavlidis: on the path of Hippocrates

→ Marc Beishon

When he's not writing ESMO guidelines or caring for patients, Nicholas Pavlidis spends time boosting the meagre training received by many of Europe's young medical oncologists. In a field of medicine where treatments can easily do more harm than good, he calls on the wisdom of a fellow Greek – arguably the first oncologist – to set his students on the right path.

“I will prescribe regimens for the good of my patients according to my ability and my judgement and never do harm to anyone” – no, this is not Nicholas Pavlidis but perhaps his ultimate mentor, Hippocrates, in part of his famous Oath of Medical Ethics. As Pavlidis, a Greek with a long-standing interest in medical history, points out, Hippocrates is thought to be the first physician to pay special attention to cancer and to clinical observation of the disease and his oath is especially relevant today for medical oncology.

Pavlidis' core interests are firmly aimed at bringing the highest standards of medical practice to bear, in line with Hippocratic principles. From his outpost on the edge of the European Union – the city of Ioannina in north-west Greece – he is maintaining a prodigious work rate in the promulgation of oncology education around Europe and the Middle East. He is also a moving force in the production of oncology guidelines, through work with the European Society for Medical Oncology (ESMO).

Together with research interests that span some of the more difficult cancer topics – including cancer in pregnancy and cancer of unknown primary origin – and a professorial position in medical oncology at the University of Ioannina, which has one of Greece's newest medical schools, Pavlidis is one of Europe's 'all-rounders'. “Indeed, if you ask me to say how I spend my time it's 25% each on patient care, education, research and administrative work,” he says.

His involvement with oncology education, in particular, is much more than just allocated time. This year, his activities include a European School of Oncology (ESO) summer school, held in Ioannina, ESMO's Lugano conference for young oncologists, and a very recent addition, ESO's Euro-Arab School of Oncology. It's been a pragmatic decision to get involved over the years in training oncologists. “After all, I do get paid to teach as part of my job. Unlike in some other countries, most professors in southern and central Europe have teaching responsibilities, and are not usually employed purely on a research basis.”



ELIGIO PAONI / CONTRASTO

However, not all professors have worked as hard as Pavlidis both at developing a model oncology curriculum and training programme at his university and also in extending expertise to other European oncologists via bodies such as ESO and ESMO. “We have to recognise that there is no homogenous teaching of oncology at undergraduate level around Europe, and a wide variation of training at the specialist stage – you need to have a structured programme in place to train oncologists,” he says. Not to mention continuing education for qualified oncologists – Pavlidis would like to see nothing short of widespread, mandatory recertification, and much more of a culture where such renewal is embraced as a learning opportunity and not a chore.

He has time to mastermind, chair and present at numerous events now, but he is the first to admit that when he returned to Greece after working abroad, back in the 1980s, the priority was to build basic capacity in his home country. “There’s no hiding that we were a poor country. When I arrived in Ioannina only 21 years ago, the situation for people was very difficult, with no local provision of a number of medical specialties, including oncology.” It was when Pavlidis saw Greeks arriving in the private wards of hospitals abroad – at the Royal Marsden in London, for example, where he worked for spell – that it was brought home to him just how badly off his country was.

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Pavlidis was actually born in Alexandria, Egypt. His Greek parents lived there for a long while, before returning to Greece when he was 13. Despite having no family medical influences, he says, "Being a doctor was the only career that struck me when I was young," and he duly went to medical school in Athens. In his third year, the St Savas Cancer Hospital in Athens took him on as a part-time assistant, which was 'great experience', and he had no other thoughts than to work in medical oncology when he graduated. "I remember how happy I was as a student to be carrying around a bottle of one of the few novel chemotherapy drugs of the day – vincristine – I thought it was a miracle for treating cancer."

He was fortunate to have the backing of a prominent American-Greek doctor, Michael Chirigos, and also of Haralambos Moutsopoulos, who subsequently moved to Ioannina. They sponsored him to spend three years in research at the National Institutes of Health in the US, where he worked on tumour immunology and autoimmunity. "One of my projects was studying how emotional stress in animals can impair their immune functions. It's an area I didn't continue but still keep track of. Of course it was Hippocrates – arguably the first oncologist – who proposed links between the melancholic personality type and illness, distinguished between benign and malignant tumours, and termed the disease 'karkinos'." (And indeed it was another Greek physician, Galen, who was prominent in taking forward Hippocrates' ideas and setting in train the 'melancholic black bile' explanation for cancer, which was to hold sway more or less for 1500 years.)

However Pavlidis wasn't side-tracked by psychoneuroimmunology, returning first to Athens to complete his internal medicine training and then on to a fellowship at London's Royal Marsden cancer hospital to train in medical oncology. "I wrote to Ian Smith, now professor of cancer medicine at the Marsden, and he invited me to train there – and it was Ian who set me onto what has become one

of my main research interests, cancer of unknown primary origin (see box p 8). He asked me to go through 100 cases and retrieve all the data, and it is work I carry on today. I also learnt how to do clinical trials."

Pavlidis returned to the St Savas Cancer Hospital to work as a senior registrar, but in 1986 was approached by Moutsopoulos, by then head of medicine at the medical school at the University of Ioannina, to set up an oncology department there. Not only was Ioannina then a very new medical school – it is one of only seven medical schools in Greece, set up in the late 1970s – but it offered an opportunity to establish cancer care in a region of Greece where there was no provision. Pavlidis says that people from this sizeable city and surrounding area – half a million people in total – had to travel several hours to Athens or Thessaloniki for treatment, or go abroad.

Furthermore, Moutsopoulos was attracting back to Greece a number of top young medics and researchers, and it was an ideal chance to combine research, teaching and clinical practice in a new environment. As Pavlidis adds, there are four cancer hospitals in Greece, but none are university establishments and none have strong research traditions. "Most major cancer research in Greece is done at university and general hospitals," he says.

By the late 1980s, Pavlidis and colleagues also had a new hospital to work in, thanks to government investment in the regions (Greece had joined the European Union in 1981, which helped with investment). "It was decided that the university medical schools needed new hospitals – and ours was built in just two years by a German company," he says. "But I started in Ioannina's old hospital with just one assistant and only four beds, and began to train young doctors and cancer nurses. Now in the new hospital we have a 24-bed ward, another ward for day treatment, and about 40 people including seven medical oncologists. We see 1,000 new cancer patients a year and the profile in our region is the usual big killers."



Despite the new facilities, Pavlidis describes the development of medical oncology at Ioannina as a ‘tremendous challenge’, but one he’s never tired of. “I’ve never thought of leaving – and after attracting young oncologists to work here we are now in the position of exporting them to other centres. Our clinical practice is now on a par with European standards.” That said, there is still more to do. “We do have multidisciplinary working but we have not yet set up tumour boards – we should introduce them,” he says.

Like many academic oncologists around Europe, Pavlidis is very unhappy about the impact of the European Clinical Trials Directive on research. “We were members of the Early Clinical Studies Group at the European Organisation for Research and Treatment of Cancer (EORTC) – I was secretary of the group for six years. It was one of the most active EORTC groups, and drugs such as Taxotere [docetaxel] were investigated first by us. But after the directive, the group had to close. We are of course part of big trials organised by the pharmaceutical companies, but this is not real research for me – I would love to go back and do novel phase I and II studies again.”

Pavlidis and colleagues are active participants in other research, notably through the Hellenic Cooperative Oncology Group (HeCOG), a collective of Greek researchers. “We were one of four founding members in 1990, and it has 15 centres now, mainly working on phase II and III trials and translational research.”

One of the research areas active at Ioannina and through HeCOG is Pavlidis’ long-term interest – cancer of unknown primary origin (CUP). Pavlidis is among the world authorities on CUP, and collaborates with the few other centres that carry out most work in the field, mainly in France, Italy and the US. Among his contributions, he is co-author (with colleague Evangelos Briassoulis) of ESMO’s CUP guidelines, and he also contributes to the START (STate of the ART oncology in Europe) and the American NCI PDQ guidelines. He has just summarised current knowledge in ‘40 years experience of treating cancer of unknown primary’ (*Acta Oncologica*, in press), in keeping with his desire to continually review and publicise current knowledge.

“It was Hippocrates who distinguished benign from malignant tumours and named the disease ‘karkinos’”

Pavlidis is also an expert on cancer in pregnancy, which thankfully is far less common than CUP. “One in 1,000 women have cancer at some point in pregnancy or in the few months after delivery. Most obstetricians will only see a few cases in a 40-year career and will be only too happy to hand responsibility over to medical oncologists.” Even so, there are estimated to be 3,500 cases in the US each year, although data collection is generally poor, and of course as Pavlidis says, it is hard to carry out extensive research on pregnant women.

As a result, as *CancerWorld* reported in a Grand Round article (Jan–Feb 2006), there is a lack of evidence and guidelines on cancer in pregnancy. Last year, recommendations were published from an expert group on breast cancer (Loibl et al. *Cancer* 106: 237-246), and Pavlidis, alone or with colleagues, has probably added more publications than most on all aspects of cancer treatment in pregnancy. A second

co-edited book – *Cancer and Pregnancy (Recent Results in Cancer Research* no. 178, eds Surbone, Pavlidis, Peccatori) – is due out this year, and there is a review, ‘Cancer and pregnancy: poena magna, not anymore’, with Ioannina colleague George Penteroudakis (*Eur J Cancer* 42: 126-140).

Turning to Latin, the authors report the ironic dual use of ‘poena magna’ – “Used by ancient scholars to describe both cancer and pregnancy: major punishment for cancer and major pain (followed by relief and joy) for gestation.” With advances in oncology, obstetrics and neonatal care, there is now considerable scope for lessening this dual pain and safeguarding the baby’s health, but more evidence is needed, and the need for top-rate communications skills for doctors is particularly acute here.

Topics such as CUP and cancer in pregnancy bring into sharp relief the depth of knowledge and judgement needed by today’s oncologists, and it

CANCERS OF UNKNOWN PRIMARY ORIGIN

“The first papers on CUP [cancer of unknown primary origin] appeared in the 1960s, when people realised that patients with metastatic disease, say in the brain or liver, did not seem to have a primary tumour,” says Pavlidis. The main problem with CUP, he adds, is that the metastases often behave in an unpredictable and aggressive manner. “It is not a rare type of tumour, as it occurs in 3–5% of cases, and is the seventh to eighth most frequently diagnosed cancer seen in a general medical oncology unit. It means, for example, we can expect to see as many as 30–40 cases a year in Ioannina.”

When patients first went to autopsy, a primary tumour was only found in half of cases. New imaging technologies – CT, PET, MRI and also endoscopy and mammography – now help to identify primary tumours, but the sensitivity and applicability of the techniques vary. “You can spend weeks trying to find a primary tumour if there are no other symptoms to guide you, such as classic indications of colon cancer.”

Recently, however, genomic profiling using microarrays has taken detection rates for the primary tumour up to 85%, says Pavlidis. “This has been commercialised in a product called CupPrint, but it is expensive and not available everywhere.”

Sadly, says Pavlidis, identifying the primary tumour rarely opens up treatment options that will alter the prognosis. “In cases such as a person in their 50s or 60s with liver metastases the survival rate is poor despite a 25–30% response rate with chemotherapy. What’s important is to split patients into favourable and unfavourable subgroups, so you don’t miss someone whom treatment will benefit – for example, women with adenocarcinoma involving only axillary lymph nodes.”

Although there are more favourable than unfavourable CUP subgroups, unfortunately the majority – about 70% – of patients fall into the unfavourable groups.

Pavlidis and colleagues continue to investigate the puzzle of CUP with clinical trials and translational research. “We are looking at gene profiles to see if there are special mutations that are responsive to targeted drugs, but so far it seems that no such mutations exist.”



Proud parents. Pavlidis (centre) poses with fellow contributors and collaborators of the comprehensive Greek-language book on Cancer in Pregnancy, which they published last year. They are all based at the University of Ioannina, and cover the fields of medical oncology, haematology, gynaecology, urology, paediatrics, pharmacology, epidemiology, bioethics, psychology, medical physics and cancer nursing

is the development of guidelines and education to raise standards that has been a major plank of Pavlidis' work for some time. He has been on ESMO's clinical guidelines group for 10 years and its chair since last year. "I know some doctors are against guidelines but I strongly believe they are there to help not only doctors as an aid to decision making, but also patients researching information, and policy makers looking to allocate resources more effectively."

ESMO's guidelines are short, mainly three-page documents, and are aimed mostly at practitioners outside of big research centres (see *Cancer-World*, March–April 2007 for more on guidelines). "One drawback of our guidelines is that they can be a year behind latest treatments – but we don't see breakthroughs every year in all the topics," says Pavlidis. Again, with colleague Pentheroudakis, he has prepared draft ESMO clinical guidelines on cancer, fertility and pregnancy, which should join the set next year.

He is also on the steering group of ESMO's educational committee, and is a long-standing member of ESO, and it is probably in education that he has made some of his biggest contributions to oncology. This year, Ioannina is hosting the

fourth ESO Oncology for Medical Students summer school, a five-day event chaired by Pavlidis that aims to cover all aspects of cancer and which works students quite hard – there are several tests to be completed.

It is a small – but so far very successful – contribution to fill one gap in a number he sees at all stages of learning about oncology. "At undergraduate level only around 40% of medical schools have mandatory oncology courses – the majority include cancer only as part of other subjects such as surgery." Not only are students missing out much information about cancer, they also lack vital exposure to aspects of care such as bedside communications skills for difficult situations. "It also matters because medical oncology is still not recognised in many countries. Where it is recognised, we see a pattern of more oncology teaching."

The state of oncology education at undergraduate level has been the subject of several reviews and initiatives in the last 20 years, but there does appear to be more momentum for change today (see also box p 10).

Pavlidis also considers that there are weaknesses in medical oncology training both in other parts of Greece and abroad. "I've tried to develop

He is highly critical of oncologists who keep trying with chemotherapy with no clinical reason

an effective programme with colleagues here – everything from journal clubs up to presenting new and difficult cases, working with pathologists. Every four months we ask our trainees to take tests – in my view it is not adequate to train people on the job without regular evaluations.”

Naturally, he is a strong supporter of ESMO's medical oncology certificate – “We have our own board test in Greece, but I'd prefer to use ESMO's” – and also the society's recertification test, MORA (Medical Oncology Recertification Approval). “The problem is that few countries have recertification schemes even where continuing education is man-

EDUCATING THE NEXT GENERATION

The lack of standards for a cancer curriculum in medical schools continues to concern oncologists. This year, Pavlidis, with colleagues from the European School of Oncology, reviewed the status of undergraduate teaching in describing ESO's own contribution, the summer schools held in Ioannina (*Cancer Treatment Reviews*, in press).

The paper reports the findings of a survey by ESO that reveals the wide variation in teaching of all the main cancer topics around Europe – information that is supplemented with details about what oncology teaching and clinical exposure the ESO students have had. It also details other initiatives to help students learn more about oncology and gives references to other papers that have looked in detail at undergraduate teaching.

Pavlidis argues that an oncology curriculum should ideally comprise epidemiology, the biology of each tumour type, patient communications, what advanced cancers can be treated successfully and how, and palliative and supportive care. “In my view this should be a mandatory curriculum for every student,” he says.

The University of Groningen and the University of Vienna run other summer schools on oncology for students. The European Association for Cancer Education, which held its 20th meeting in the UK this June, is a good source of information (see www.eaceonline.com); the WHO Collaborating Centre for Cancer Education is based at the University of Groningen and has a project for medical schools (see <http://who-ccce.globalink.org>).

datory,” he says. “It will be much easier if we all move to a standard mandatory system, like in the US” (where maintenance of certification in medical oncology is required by the American Board of Internal Medicine, although only every 10 years).

A body called the Accreditation Council of Oncology in Europe (ACOE) is active now in assessing credits, and both ESMO and the Federation of European Cancer Societies (FECS) have carried out research on the continuing medical education picture in Europe, including inventories of the policies in all countries.

ESO's masterclasses also offer solid continuing medical education, and Pavlidis is to be found as a chair and presenter at most events. His involvement with ESO goes back to the 1980s. He took the first course held outside of Milan, and thanks to his presence in Greece was asked to promote educational activity in the Balkans and now the Middle East, as the school has further expanded its activities. “The Euro-Arab School of Oncology is very new – we held our first meeting last year and it was attended by over 100 people. The region is hungry for education.” The first masterclass, chaired by Pavlidis of course, takes place in Cairo this September.

Not that Greece is as far along as he would like. If he could make one big change, it would be to introduce a proper cancer registry in the country, as its present system is inadequate, he reports. And although healthcare provision has improved greatly in Greece over the last 30 years or so, the cancer ‘taboo’ is still very much in evidence, in common with other southern European countries. “It is relatively recently that we now always discuss the diagnosis with patients and families, as we cannot collaborate with them otherwise,” says Pavlidis. “But we do not often talk about the prognosis, especially if it is bad – we do try and sugar the pill.” He is, however, highly critical of oncologists who keep trying with chemotherapy with no clinical



Proud grandparents. Pavlidis and his wife Marilena (far right), with their son Antony, daughter Vicky and grandson, who had just been christened 'Nicholas'

reason. "It's not common, and I understand that some oncologists become emotionally driven. But apart from treatment effects it can mean a big waste of money."

Greeks are notoriously resistant to health promotion messages. Pavlidis says smoking rates are still very high – the highest in Western Europe – and diets are not as healthy as they were. 'Magic' remedies for cancer and other illnesses can quickly grip the nation – a recent example from this year being widespread publicity for a concoction of olive leaves that led, in one sad case, to a man shooting dead his brother over an argument about administering it to a third brother suffering from cancer. Meanwhile, olive leaves were changing hands for 60 euros a kilo in markets.

That sort of news could make Pavlidis retreat into his shell – or shells that is – and what a distraction. He has a major hobby as a collector of mollusc shells and has amassed a huge collection, much of which is now exhibited in two locations in and near Ioannina. He gives talks not only on their biology but also on the relationships, through the

ages, between shells and people. While the collection was growing at home it did emit a pungent aroma, somewhat testing the patience of his wife, Marilena, and his two children, who are both in the UK at present – Vicky (a psychologist) and Antony (training in internal medicine but heading for cardiology).

Pavlidis continues to juggle his many commitments, but still finds time to investigate and think about what can be seen as some of the deepest issues in cancer – such as the similarities between embryogenesis and carcinogenesis, and the different manifestations of ostensibly the same tumours in the young and old.

They are the kind of questions that may well have appealed to Hippocrates. Pavlidis has a talk that shows how he worked as a cancer pathologist, epidemiologist, clinician and medical oncologist some 2,500 years ago. Perhaps Hippocrates' most far-sighted quote, not least when it comes to cancer, is: "It is more important to know what sort of person has a disease than to know what sort of disease a person has."