From bench to bedside and back?

US academic health centres face challenges that may threaten the future vitality of the clinical research enterprise, but they are fighting back, says Diane Gershon.

At a time when public and private support for biomedical research in the United States is robust and the opportunities for biomedical advancement never greater, some of the nation's most prestigious research hospitals are financially ailing. These fiscal difficulties may be lessening the ability of the nation's 125 academic health centres (AHCs) to conduct clinical research and nurture the careers of the very cadre of researchers best positioned to translate basic research into clinical practice.

AHCs, which comprise medical schools and their affiliated teaching hospitals and faculty groups, straddle and integrate basic and clinical research. They provide an environment where basic and clinical researchers can rub shoulders and transfer what is learned at the bench to the bedside.

AHCs conduct nearly 30% of health-related research in the United States, according to a 1999 report, *From Bench to Bedside*, by the Commonwealth Fund Task Force on Academic Health Centers. In addition to research, AHCs also train health professionals and biomedical researchers, provide patient care and conduct community outreach.

Having a stab: some academic health centres are creating a more industry-friendly environment in which to conduct clinical trials.

The aspect of clinical research that seems most threatened is 'translational' clinical research, according to David Nathan, president emeritus of the Dana-Farber Cancer Institute in Boston and professor of paediatrics at Harvard Medical School. He defines translational research as studies in the lab that are brought directly to the patient to improve either diagnosis or therapy. And it is the cohort of clinical researchers doing translational research, with a foot in the laboratory (and a reasonable grasp of basic research) and a foot by the bedside studying patients, that seem to be in short supply, he says.

The financial pressures facing some AHCs can be blamed, in part, on the advent of managed care in the United States during the 1990s. "It's not hard to show that these institutions [AHCs] are economically more pressed, at least on the clinical side, than they have been before," says David Blumenthal, director of the Institute for Health Policy at the Massachusetts General Hospital/Harvard Medical School. But to go from there and show that the central missions of the AHCs are compromised is more difficult, he says.

AHCs facing financial pressures have responded by cutting programmes, reducing workforces and selling teaching hospitals. Some AHCs are also creating a more industry-friendly environment in which to conduct clinical trials in the face of aggressive competition from for-profit entities (see page 6).

HARD ROAD TO HOE

Reduced clinical revenues from faculty group practices and affiliated teaching hospitals has meant less money in the pot for the cross-subsidy of clinical research and training. Moreover, in highly managed markets in particular, clinical faculty — especially junior faculty — are under increased pressure to devote more of their time to patient care and less to activities involving teaching and research.

Physicians contemplating a career in clinical research face endless training periods and enormous medical school debts. In 1999, the average medical school debt was about $91,000, according to Stephen Heinig, senior staff associate in the Division of Biomedical and Health Sciences Research at the Association of American Medical Colleges (AAMC). Moreover, given concerns about the sustainability of such a career and the lure of higher incomes in clinical practice, it is not difficult to see why many physicians

turn their back on a career in clinical research.

Alarm bells first rang over the potential shortfall in clinical researchers over 20 years ago when James Wyngaarden spoke and wrote of the clinical investigator as an 'endangered species'. Clinical research was not helped when AHCs built up their capacity for basic research in the 1980s and 1990s. "I think AHCs are representative of the culture of science in the biomedical area and they have been infatuated with molecular biology for the past 20 years," says Blumenthal.

National Institutes of Health (NIH) grant applications from physician-scientists have remained roughly steady for the past 20 years, says Blumenthal. However, the implications of doubling the NIH budget may provide 'a strong argument' to increase the supply of people who could translate the growing body of research funded by NIH largesse into clinical practice, he says.

A BRIGHTER FUTURE?

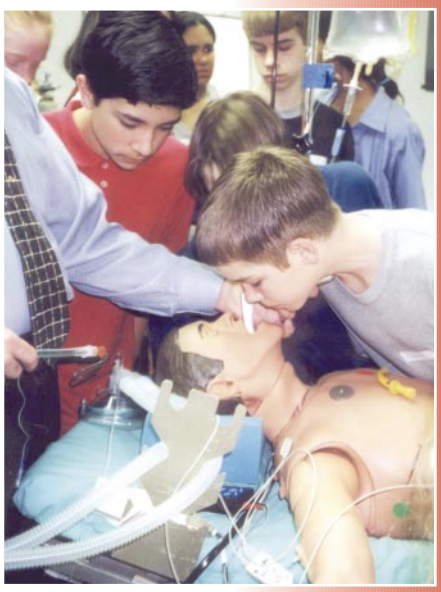
AHCs may not be out of the woods financially, but the NIH's prosperity may help ease the situation. The agency has introduced several initiatives in the past few years aimed at creating a more hospitable environment for physicians pursuing a career in clinical research. These include the mentored, career development award (K23), designed to kick-start the careers of young investigators involved in patient-oriented research, the mid-career development award (K24) and the clinical research curriculum award (K30) given to institutions not individuals.

The K23 award is an "important recognition point and it provides [clinical researchers] with protected time", says Roger Meyer, the AAMC's senior consultant for clinical research in the Division of Biomedical and Health Services Research. The K23 award allows individuals to spend three-quarters of their time on research, away from patient-care duties, which is necessary if they are going to compete successfully for an NIH-supported RO1 grant, he says.

The University of Colorado Health Sciences Center in Denver, Colorado, was one of the lucky recipients of an institutional K30 curriculum award and for the past two years has offered both doctoral and certificate programmes in clinical science for the advanced training of physicians and healthcare professionals. "The NIH award mechanisms have truly come to our rescue," says Laurie Shroyer, associate director of the PhD Program in Clinical Science. The award was essential in getting the certificate programme underway, she says.

The clinical investigation track of the PhD programme, for example, has a strong mentoring component and builds proficiency in areas such as biostatistics, clinical epidemiology, clinical trial design, grant writing, biopharmaceuticals and pharmacokinetics. Although off to a good start, the uptake for these programmes, particularly among physician fellows, is not as uniform as Shroyer would like. Depending on their financial status, support for students varies across departments and divisions, she says.

The prospect of the introduction of an extramural, NIH-funded clinical research loan repayment programme (one already exists for intramural researchers) is also energizing the community and would provide the welcome relief from educational debt that prevents so many from contemplating a clinical-research career. Congress authorized the programme late last year as part of the Clinical Research Enhancement Act and Pediatric Research Act. For every year of service as a clinical researcher (up to a maximum of three years), it would allow the NIH to repay up to $35,000 of an individual's educational loans. the NIH must still devise an implementation strategy for the programme, which is unlikely to start before 2002 as no funds were appropriated for 2001.



Putting your money where your mouth is: an NIH-funded programme offers to repay clinical education debts to encourage new trainees.

CATCH 'EM YOUNG

Some evidence indicates that individuals make career choices at an early age. With this in mind, institutions, such as Wake Forest University School of Medicine in Winston-Salem, North Carolina, now run professional development programmes for science and maths teachers in the community. The programmes at Wake Forest, for example, are undertaken in partnership with the local school system and the historically black Winston-Salem State University, and are geared towards closing the performance gap in maths and science education.

In addition to these community outreach initiatives, Wake Forest also strongly encourages students to gain research experience while in medical school. About one-quarter of the freshman-class students do a summer research rotation, the majority are in clinical research, and all medical students must complete an independent science-study before graduation.

Some of the foundations are also getting in on the act. The Doris Duke Charitable Foundation, for example, already offers two career-development awards aimed at strengthening and revitalizing clinical research. The foundation's newest programme will enable students to take a year off medical school and obtain some didactic and 'hands-on' clinical research training, as well as undertake a mentored clinical-research project. And the Damon-Runyon-Walter Winchell Foundation has received a $15-million grant from Eli Lilly to help revive clinical investigation in cancer.

More support, from the NIH, foundations and the AHCs themselves along with a debt-repayment plan, may yet revive an ailing part of the biomedical research enterprise in the United States. ■

Diane Gershon is Assistant Editor, New Technology at *Nature Medicine*.

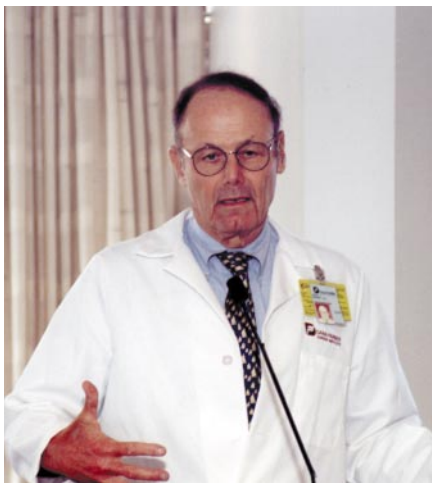
Some evidence indicates that individuals make career choices at an early age.

The movement of clinical trials from the public to the private sector is forcing academic health centres to re-examine their role.

Traditionally, drug companies both managed and sponsored clinical trials while academic health centres (AHCs) conducted them. But times are changing. Drug companies, under increasing pressure to find ways to cut costs, create efficiencies and reduce time-to-market, are increasingly opting to outsource the management of clinical trials to commercial entities. Many of the trials are now taking place in venues other than the AHCs, such as community hospitals, which are competing hard for a share of the clinical-trials market in much the same way they already do for patient care.

New for-profit players have entered the marketplace over the past two decades and include contract research organizations (CROs) and site-management organizations. There are even companies that match drug companies with CROs in an effort to streamline the outsourcing process. Although outsourcing of clinical trials is creating new jobs, a job in a CRO will not suit everybody and not everybody will thrive in such an environment. "It is a changing environment and so it's important to be able to cope with change and also be very solutions-driven," says Helen Wyn Davies, senior vice-president of clinical development services at Quintiles, the largest drug CRO in the United States. Moreover, as this is a service industry, "you're viewing life very much in terms of a provision of a service," she says.

The CRO industry draws a high proportion of its employees (about 80%, according to Joseph von Rickenbach, chairman and chief executive of Parexel, one of the top three drug CROs in the United States) from the pharmaceutical industry. There, it is not uncommon for individuals to focus on one therapeutic area and be assigned to a particular study for years at a time. One of the benefits — and challenges — of working within a CRO is that the companies offer the chance to work on several different therapeutic areas and studies, and with a range of clients, within a short space of time.



Paediatrician David Nathan believes the AHCs should be at the cutting edge of research, not running big clinical trials.

It was just such an opportunity that attracted Gary Gartenberg to Covance two-and-a-half years ago. He had been in private medical practice for 20 years before deciding on a career move. "It's been very motivational to be involved in a company that cuts across the entire industry," says Gartenberg, one of 15 physicians in the clinical-development team that designs and reviews the protocols and deals with the trial's medical aspects and safety monitoring.

Although working with CROs provides variety, the job has disadvantages as well. For example, publication opportunities are fairly limited. "It doesn't happen as often as I would like," says Raul Valentin, vice-president of human resources for Covance's Clinical Development Group. As all CROs operate under strict confidentiality agreements and non-disclosure policies, clients must consent to publication of any information deemed proprietary.

REGAINING LOST GROUND

While some CROs continue to expand their global reach, and are moving into areas such as discovery, product development, manufacturing and sales, AHCs are rethinking their provision of clinical services. In an effort to create a more industry-friendly environment, some AHCs have formed centralized clinical-trial units to address the issues concerning patient recruitment times, delays in institutional review-board approval, quality assurance and higher costs that are causing drug companies to go elsewhere.

Some institutions have established formal relationships with CROs in the hope of expanding their access to industry-sponsored trials. Parexel's oldest and most successful alliance is with Humboldt University. "It's so intimate that our company has several hundred employees on campus in Berlin," says von Rickenbach, and physicians at the university can intern with Parexel. von Rickenbach admits, though, that forging such partnerships can be arduous work. "We are a commercial company… and academic centres are not. Their primary purpose is not to earn a return to shareholders and to get these two purposes… onto a common denominator is not easy," he says.

Indeed, not all such partnerships prove fruitful. Three years ago, Johns Hopkins Medical Institutions entered into a non-exclusive agreement with Quintiles. Johns Hopkins hoped that Quintiles would steer more clinical studies its way and in return Quintiles would have the name recognition of Hopkins and access to its top clinical investigators. "In reality [Quintiles] didn't give us anything and they weren't very interested I think in developing a real lasting relationship," says endocrinologist Adrian Dobs, at Johns Hopkins. The partnership has since fizzled out.

CROs generally feel that AHCs are basically too slow for them, says Dobs. "We appreciate that and we are trying our best to do better but we're under different constraints," she says. Johns Hopkins established a clinical-trials unit about two years ago. The unit helps sponsors identify investigators but also offers investigators a way to improve how they market their expertise. But as the line between publicly funded and privately sponsored research blurs, issues of academic freedom and conflict of interest need to be worked out more carefully, says David Nathan, president emeritus of the Dana-Farber Cancer Institute in Boston and a paediatrician at Harvard Medical School.

"If universities get involved with it for the money, I worry about that too because it's not really the academic mission," he says. "The science is moving like mad. It's extremely exciting and I think that's where the AHCs should be, not running big clinical trials."

D. G.

Too few doctors in the house

Increased demand by public healthcare for an already dwindling number of doctors has resulted in a low supply of clinical researchers in France, says Catherine Tastemain.

With the falling number of graduate doctors, the growing lack of qualified 'back-up' staff and a university hospital system hardly conducive to the setup of clinical trials, French public clinical research is in a predicament. "Any young doctor who wants to pursue clinical research certainly has his work cut out for him," says Christian Funck-Brentano, a clinical pharmacologist at the St Antoine university hospital centre in Paris, who also heads the hospital's clinical investigation centre (CIC). His colleagues heartily agree. Young graduates have to overcome countless hurdles if they want to pursue clinical research in a public hospital and solutions do not seem to be forthcoming despite the incentives that the authorities have deployed over the past few years.

Until 1970, France was churning out roughly 10,000 physicians a year. But in the early 1980s, a competitive end-of-year examination was enforced for first-year medical students. That test has greatly reduced the supply of potential physicians. Since 1985, a mere 3,500 doctors have been trained per year. "Today's predicament is that there are just not enough of us to care for the patients," pointed out Marc Beaussier, a young anaesthetist at St Antoine hospital.

So, as a 'hospital practitioner', he is having an even harder time undertaking clinical research. In France, hospital practitioners, who only receive their stipend from the hospital, are 'encouraged' to do clinical research even though their professional status does not include research. When Beaussier wants to start a clinical investigation, he must take time off his medical practice at the hospital.

However, protocols take time to put together, administrative delays take forever and the qualified staff that could help him design the project, collect the data and analyse research findings are lacking. "It's very long and very complicated and nobody will pay the hospital back for the time I'm going to spend doing all this myself," says Beaussier.

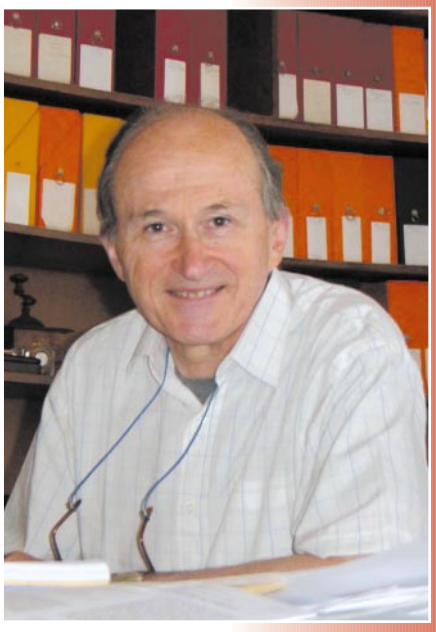
Actually, hospital practitioners who want to undertake clinical research do have a solution — to become a senior lecturer or university professor combining the university and the hospital. If they succeed, they are required to devote 50% of their time to teaching and research. In practice the figure is usually 20% or even 30% because of healthcare needs.

Also, universities emphasize some kinds of research over others, says Jean-Claude Dussaule, a physiologist at St Antoine. "Clinical research is easy to get started when it addresses a drug because trials are heavily backed by the pharmaceutical industry," he says. "On the other hand it's all uphill for clinical research on physiopathology."

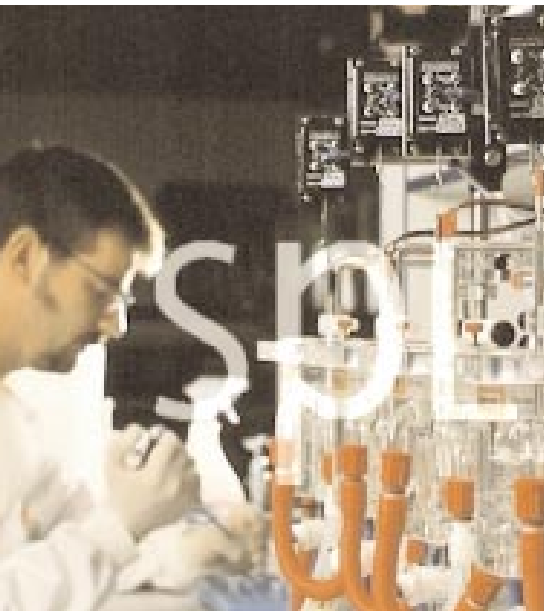
FRENCH PHYSICIANS FLEE PHARMA

From 1980 to 1995, many highly qualified public-sector doctors turned to private pharmaceutical R&D because of higher salaries and the attraction of responsible positions. The stream of physicians flowing into this private industry has now dwindled. Current job offers are not considered very gratifying for doctors and, above all, hospital demand is now high because the country has fewer doctors. But the opportunities for young scientists are still attractive.

Emmanuelle Le Gorfec, a young biostatistician in her third year working for a private pharmaceutical company, said: "Here, the pay and recognition are better whereas at the university or public research organizations



Joël Ménart, head of clinical research, Paris Public Hospitals, believes that poor organization, not lack of funds, is the major obstacle to clinical research in hospitals.



SPL

Young graduates have to overcome countless hurdles if they want to pursue clinical research in a public hospital.

you're just one in a thousand."

The pharmaceutical industry has, of course, maintained its close ties with public hospitals, especially university-hospital facilities, with the industry funding a large share of the clinical trials of drugs. Increasingly, contract research organizations (CROs, see p.6) are standardizing operational protocols. Hospital clinicians generally admit that, overall, CROs with more resources on tap than public hospitals do their job well. However, a trend has surfaced over the past several years. Although the pharmaceutical industry has kept clinical trial centres in Western Europe (because the drugs are mainly sold in these countries), the industry is organizing more clinical studies in the former Eastern Bloc.

HOSPITALS SOLD SHORT

In contrast to this excess of riches in CROs, Joël Ménart, the top official in charge of the Clinical Research Division, Paris Public Hospitals, notes that clinical research at hospitals tends to get short shrift. The problem, he says, is that researchers at university hospitals must divide their time among teaching, care, research and administration simultaneously. Ménart thinks that, instead, clinicians should rotate from duty to duty in shifts, rather than juggle them all simultaneously. "I'm not saying it's easy to organize. It would probably take several years to set up," says Ménart.

Although Ménart's proposed reform is not yet being considered, other changes have been gradually introduced over the past several years, but to limited effect. For example, the government decided to set up CICs in some hospitals to bring together hospital departments and research units from Inserm, the French national institute for health and medical research.

Although far-reaching, the changes have not been enough to turn the situation around. The 17 CICs now in place cannot realistically be considered as providing enough outlets for young physicians. Many doctors — even the ones working at a university-hospital centre — feel that there is a conflict between hospital budget constraints and the cost of clinical research. "The authorities can't tell us that the prescribed antibiotics are too expensive out of one side of their mouth and announce a several million-franc investment in clinical research out of the other," said Beaussier.

Ménart disagrees. The clinical-investigation budget is negligible compared to the budget allocated for care. "If you tap into every possible funding source, you get an overall appropriation of roughly 150 million francs (US$19.5 million) — not including the wages for 3,000 university-hospital teachers — whereas health expenditures are at a hefty 696 billion." He believes that in any case the budget is not the primary hurdle for clinical research in hospital but rather the poor organization of the university-hospital system. ■

Catherine Tastemain is a science journalist based in Paris.

UK WORKING FOR A BETTER CLINICAL CLIMATE

For the past three years, the Wellcome trust has been funding the building and equipping of clinical research facilities in several UK universities.

WELLCOME TRUST

Rarely have areas of basic science been more ripe for development into applications than those of the molecular genetics and biology flowing from the human genome project. Yet there is a global lack of the clinical research pivotal to the transformation. "Less is being done, and it is less well done," says Helen Cope of the Clinical Careers Initiative at the Wellcome Trust.

In an attempt to reverse this trend in Britain, the Trust has for the past three and a half years been funding the building or refurbishment and equipping of clinical research facilities in Birmingham, Cambridge, Edinburgh, Manchester and Southampton. The National Health Service Trusts will pay the running costs, including salaries for core staff, such as research managers and nurses, while the research councils will pay for the research through grants to clinical researchers at the universities.

The aim of the initiative is to bring the clinical and academic worlds closer together, something that is essential, says Cope, if the science emerging from the human genome project is to reach patients. Yet the facilities alone will not be enough. Doctors pursuing serious research usually take longer to reach consultant level than if they followed a service role within the NHS. Both the Wellcome and the Medical Research Council attempt to make the research option more attractive by offering fellowships.

Several diploma and masters courses in the United Kingdom give an overview of drug development for anyone working in clinical research or some other aspect of drug development within any clinical organization.

If a drug is to be licensed for use, each step of the process must also satisfy the regulatory authorities. "Regulatory affairs is a growth area and will continue to be," says Nicky Lilliott, of the Association of British Pharmaceutical Companies. Helen Gavaghan

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