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From ECR 2008: What did you learn in school today?

Peter A. Rinck

In my leisurely hours of continuing education in February and March, I read some articles in the daily papers and learned journals that taught me new aspects of medicine. Among them were the following issues.

We learned in medical school that high cholesterol (i.e., LDL cholesterol) will kill you. We have to lower it. Now we hear with increasing intensity that LDL cholesterol may not be the cause of atherosclerosis and coronary heart disease. It must be something else, and the question is what.

Recent evidence boosts the conclusion that statins, drugs used to lower cholesterol production, restore and improve endothelial function directly. Medical teaching that cholesterol plays a key role in heart disease is open to question. Although scientific publications suggested for quite a while that cholesterol might not be the responsible foe, the public health dogma was never touched.

Among the many agents sold to lower cholesterol are two drugs, ezetimibe and simvastatin, that operate on different mechanisms. When one of the major pharmacological players in the field combined them into a single medicament, the researchers found that cholesterol was lowered more than with one drug alone. The combination did not, however, accelerate the slowdown of fatty plaque accumulation in the arteries.

I was curious and went a long way to get the physician's prescribing information of the medicament where one reads: “No incremental benefit of [the combination medicament] on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.” [1]

What did we learn?
Back to the drawing board.

Next topic: For decades I have followed the debate over diagnosis and treatment of prostate cancer: Operation is best. Radiation is best. Seeds are best. Hormones will heal you. It always depended on the eye of the medical beholder. Fifteen years ago, substantial controversy existed about the advisability and effectiveness of screening programs, the most appropriate staging evaluation, and the optimal management of patients with all stages of prostate cancer. There were inherent ambiguities in recommending staging and treatment choices [2].

Some weeks ago, the U.S. Agency for Healthcare Research and Quality issued a review of prostate cancer treatments, including surgical removal, radiation, hormone therapy, and “watch and wait,” which involves careful monitoring but no active treatment until the cancer shows signs of growing.

Because none of these treatments emerged as superior, the agency came to the troubling conclusion that it could not recommend one over the others [3].

What do you tell people who come to you, although you're are only a radiologist, and ask what treatment you would propose or consider?

What did we learn?
Back to square one.

If now you get depressed and want to get happy again with Prozac, the antidepressant taken by some 40 million people worldwide, it will be cheaper for you to take a placebo or a glass of wine. Using the Freedom of Information Act, Irving Kirsch from the University of Hull and colleagues in the U.S. and Canada could access all clinical data submitted by the drug producer to the FDA. Apparently, some studies had not reached the public [4].

The authors summarized their results: Drug-placebo differences in antidepressant efficacy increase as a function of baseline severity but are relatively small even for severely depressed patients. The relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication. In understandable words, there is hardly any difference between placebo and medicament.

Such abrupt revelations are major changes for diagnostics and treatment entrenched for decades.

■ What did we learn?
We should ask ourselves: What comes afterwards? How do we react to developments like these? Of course, things like these never happen in radiology – at least, nobody talks about it.

■ What else did we learn?
Always look on the bright side of life.

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If it moves radiologists will want to screen it

Peter A. Rinck

Six years ago I wrote a column about screening programs, stating that screening approaches that are not based upon firm foundations become ideological crusades. The outcry was earsplitting. Somebody delivered a broadside against me claiming I would undermine dozens of years of hard work in mammography.

"Don't make promises you can't keep … screening doesn't make people immortal."

I had pointed out that it was neither my business nor my intention to either bless or damn the use of screening in those groups that would benefit from, in that particular case, x-ray mammography.

"A critical approach is necessary," I wrote. "Two points should never be forgotten: The screening procedure must have a clear advantage for the person screened, and the population must not be left in doubt about its reliability. If these philosophies are not adhered to, the public will lose faith in the screening test and in the people proposing and performing it... I believe that screening in general is an important and necessary task for medical professionals." [1]

What has happened in half a decade? Nothing much has changed in mammography. The U.S. National Cancer Institute summarizes the state of affairs:

"Several large studies conducted around the world show that breast cancer screening with mammograms reduces the number of deaths from breast cancer for women aged 40 to 69, especially those over age 50. Studies conducted to date have not shown a benefit from regular screening mammograms, or from a baseline screening mammogram (a mammogram used for comparison), in women under age 40." [2]

Lung screening is different. "Are you a smoker? Then you are at high risk of contracting lung cancer! To rule out cancer at a very early stage you should periodically undergo CT-based screening, a low-dose x-ray examination of your lungs costing less than €250 (tax included)!"

I have slightly re-phrased this advertisement seen in a private radiology office somewhere in Europe. I found it unpleasantly close to the edge of being unethical. Many private radiologists are in tough straits, anxiously looking for increased returns on their heavy investments in multislice CT (MSCT) and high-field MRI.

But would I, the leading hypochondriac in town, undergo such an examination? Yes! Immediately! Lung cancer is one of the leading causes of cancer death, and those at greatest risk are identified readily on the basis of age and smoking history. By the way, I don't smoke – unless I am given a Havana cigar.

The radiologist's argument in favor of his offer, which is not reimbursed by any health insurance in his country of residence, is that MSCT will identify small lung lesions at a higher rate than chest x-ray. The individual can then be treated and saved from dying of cancer.

The problem is that there is no proof. On the contrary, the 20-year follow-up of the Mayo Lung Project showed no statistically significant reduction in lung cancer mortality among men who had been offered intense screening compared with those who had not. It additionally suggested that some lung cancers detected through screening have limited clinical relevance [3].

The authors of this follow-up study pointed out that their findings only added to the controversy surrounding low-dose MSCT as a lung cancer screening test. They noted that if lung cancer lesions with limited clinical relevance truly exist, then CT may do more harm than good [3].

Other research groups have emphasized this point. Dr. Peter Bach and colleagues at the Memorial Sloan-Kettering Cancer Center in New York City observed that while screening for lung cancer with low-dose CT may increase the rate of lung cancer diagnosis and treatment, it may not lead to a meaningful re-

duction in the risk of advanced lung cancer or death from lung cancer. They stressed that until more conclusive data are available, asymptomatic individuals should not be screened outside of clinical research studies that have a reasonable likelihood of further clarifying the potential benefits and risks [4].

Prof. William Black, director of chest radiology at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire, added his views in a review paper. He noted that CT screening can cause additional harm, for example, from false-positive test results and overdiagnosis [5].

Even worse, the talk of the town at the 2007 annual meeting of the RSNA in Chicago was an article that had just been published in The New England Journal of Medicine. The paper discussed the growth in the use of CT and the increase in patient radiation exposure. It claimed that CT scanning could be responsible for as many as 2% of all cancers diagnosed in the U.S. over the next 20 to 30 years [6].

The next step is whole-body scanning. If your health, and that of your partner, your children, your parents, and your in-laws is at stake, a guilty (though misguided) conscience will nag: "Perhaps I should offer them such an examination. Let's keep out of harm's way and get peace of mind. What can we lose?"

Turning medicine or, in this instance, radiology, into an exact, predictive science will not work, because that is not what medicine is. When you read the hundreds of images of a whole-body study carefully enough, you will find something "abnormal" in any asymptomatic person. Then what do you do? The easiest way out is to overlook that finding or propose a reexamination in six months' time.

That is unethical. The study was unethical too. Two unethical things don't cancel each other out. Otherwise you have to kick off an avalanche of additional tests. Half a year and €50,000 later, you can tell the client (now a patient) that he/she is healthy – except for the laparotomy scar and the sleepless nights due to worry. There was no peace of mind; quite the contrary. One passes quickly through a gray zone into screening techniques that have no evident benefit for the person studied.

Screening is a little like playing the lottery; you might win, or you might lose. Whole-body CT or MRI screening belongs to these lotteries. Its only advantage over plastic surgery is that you will not die on the table.

Screening differs from clinical practice. It targets apparently healthy people, offering to help individuals make more informed choices about their health. The U.S. Food and Drug Administration (FDA) offers the following advice:

"Taking preventive action, finding unsuspected disease, uncovering problems while they are treatable, these all sound great, almost too good to be true! In fact, at this time the FDA knows of no scientific evidence demonstrating that whole-body scanning of individuals without symptoms provides more benefit than harm to people being screened. The FDA is responsible for assuring the safety and effectiveness of such medical devices, and it prohibits CT manufacturers from promoting their systems for use in whole-body screening of asymptomatic people. The FDA, however, does not regulate practitioners, and they may choose to use a device for any use they deem appropriate."[7]

Drs. David Brenner and Eric Hall from the Center for Radiological Research at Columbia University in New York concluded in the NEJM paper that, "When a CT scan is justified by medical need, the associated risk is small relative to the diagnostic information obtained. However, if it is true that about one-third of all CT scans are not justified by medical need, and it appears to be likely, perhaps 20 million adults and, crucially, more than one million children per year in the U.S. are being irradiated unnecessarily."[6]

Many different organizations have set up straightforward criteria for screening, including the World Health Organization and the U.K. National Screening Committee [8,9]. The following are taken from the U.K. criteria:

- The condition should be an important health problem.
- The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood, and there should be a detectable risk factor, disease marker, latent period, or early symptomatic stage.
- There should be a simple, safe, precise, and validated screening test.
- There should be an agreed policy on the further diagnostic investigation of individuals with a positive

test result and on the choices available to those individuals.

- There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

- Clinical management of the condition and patient outcomes should be optimized in all healthcare providers prior to participation in a screening program.

- There should be evidence from high-quality randomized controlled trials that the program is effective in reducing mortality or morbidity.

- There should be evidence that the complete screening program (test, diagnostic procedures, treatment/intervention) is clinically, socially, and ethically acceptable to health professionals and the public.

- The benefit from the screening program should outweigh the physical and psychological harm (caused by the test, diagnostic procedures, and treatment).

- The cost of the screening program (including testing, diagnosis, and treatment, administration, training, and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e., value for money).

- Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.

Yet the public health environment insists that lung or whole-body screening is a public health issue that should not be questioned. Skepticism, even when endorsed by scientific results, might just delay action; and any action is good. They don't see that action for the sake of action can be very harmful.

When lining up for the security check at an airport a few weeks ago, I suddenly thought, "This is like medical screening, so the outcome should be assessed like that of medical screening." I checked the literature when I came home and found that somebody else already had had the idea. A U.S. group had published a paper on it [10].

Approximately 2000 people have died as a result of explosives on airplanes since 1969. A similar number have been killed in attacks on trains. Yet there is no screening of railroad passengers, apparently without major harm.

The authors argue that by analogy, in medical screening this would be like screening the left breast with x-ray mammography but not the right breast. They concluded: "Of course, we are not proposing that money spent on unconfirmed, but politically comforting, efforts to identify and seize water bottles and skin moisturizers should be diverted to research on cancer or malaria vaccines."

The manner in which airport checks are performed resembles the comment made to me by a patient regarding his annual prostate examination. "I always go to my prostate screening; therefore I have not gotten cancer," he said.

The "therefore" is wrong. There is no causality between making visits to the doctor and getting cancer.

On the other hand, remember the story of the man who entered the U.S. and after the security check was told: "You should get the opinion of a real medical doctor concerning your prostate as quickly as possible."

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Radiologists meet with heavy collateral damage

Peter A. Rinck

I was at a large brasserie in Paris a few weeks ago. Looking for the toilets, I passed by a blackboard with information for the waiting staff. The advice for the day: "Push the fresh fish!"

The waiters did. I ordered steak.

Nearly one-third of the world's fish consumption stems from offshore farms, mostly in bays and estuaries along the sea coasts. In Europe, industrial salmon farming used to be a Scandinavian business. Nowadays, a Norwegian company dominates the world salmon farming industry, from Norway to Scotland, Canada, and Chile. Fish farming has grown into a sophisticated industry that aims to profit from scientific and technological advances.

I was first exposed to aquaculture when a research team at our institute was contracted to perform high-resolution MR spectroscopy and imaging on salmon. The salmon farmers were disturbed to find that live fish transported in tanks were losing their taste. MRS revealed changes to the chemical composition of the meat, changes that were blamed on the fish being stressed. It was suggested that valium added to the water could calm the fish, prevent these changes, and make the salmon tastier.

I do not know whether the producers ever implemented this solution. Salmon farmers claim not to use hormones, but they do employ fungicides, pigments to artificially turn the white flesh of farmed fish wild salmon red, and antibiotics. The dosages stay within legal limits that vary from country to country [1]. The industry had been criticized for their ecological effects on the environment, and a risk-benefit analysis has suggested that consumers should not eat farmed fish from Scotland, Norway, or eastern Canada more than three times a year (!) to minimize the possible health hazard [2].

Risk-benefit management is part of the curriculum at all business schools. In the case of fish farming, it means the best shareholder value for the best possible quality and highest quantity of salmon. The question is how many chemicals and antibiotics, if any, are needed to reach this objective.

A similar situation holds for the healthcare industry. During the past 30 years, there have been major developments in medical imaging. Many have been transformed from research into medical reality through major investment by companies. These developments often carried major business risks. Other risks, deemed minimal, were sometimes deliberately overlooked.

Risks were sometimes deliberately overlooked. Warning voices were not heard.

Side Effects

In late summer 1988, exactly 20 years ago, I saw a poster at a major scientific meeting in Berlin. I still remember it – hanging close to one of the big windows in a corridor of the conference hotel.

The paper was about the incorporation of gadolinium into bone, a topic of limited interest to most congress participants because the newly developed gadolinium contrast agents were known to be stable and safe despite the toxicity of their prime component, gadolinium. Free gadolinium is deposited in the liver, bones, skin, and lymph nodes. Therefore it has to be tightly held by a claw, a chelate. These chelates characterize and differentiate the various contrast agents from each other. Basically, they come in two configurations: linear, as for instance in Magnevist and Omniscan; and cyclic, as in Dotarem or Prohance.

Although they are considered unspecific contrast agents, the target organ of these compounds is the kidney, and they require proper renal function to be excreted. Any problem with the kidneys will leave residues in the body.

The stability of the different gadolinium chelates in the body varies drastically. All release gadolinium ions, but some substantially more than others. As a precaution, additional chelate is part of the contrast agent mixture injected – to try to catch the free

gadolinium in the patients' bloodstream. Linear agent O dissociates in 30 seconds and releases the gadolinium ion, linear agent M in 10 minutes, and cyclic agent P in three hours [3]; cyclic agent D remains undissociated for many hours. It would be advisable to use agent D in patients whose kidney function is impaired. Unfortunately, the latter agent was and is available only in Europe, not in the U.S. because somebody there blocks the patent.

Rumor has it that one of the companies with a linear agent had the choice: linear or cyclic. They went for linear, most likely because they could market it faster at lower cost.

Magnevist was the first agent on the market, in 1988. It was followed by Dotarem the year after, Prohance in 1992, Omniscan in 1993, and Optimark in 1999. To date, more than 200 million examinations with such agents have been performed worldwide.

By the late 1980s, all relevant details about these contrast agents were included in our MR imaging teaching courses. Special courses for employees of pharmaceutical companies were available, too. I received a call from one manufacturer following such a course, complaining that I had stated that their compound had led to fatal reactions. I had never made any such statement. I had explained that any injection, be it of a contrast agent or water, may have immediate, acute side effects, for instance, anaphylactic shock.

With hindsight, I wonder whether they were afraid of something – because it had been pointed out as early as in 1988 at a conference in Norway that a macrocycle approach to contrast agents would create inert gadolinium complexes [4]. At that time, no manufacturer ever spoke about the possibility of unknown or unexpected late effects, although the drama surrounding the x-ray contrast agent Thorotrast should have been well remembered [5].

Applications Expand

The years passed, and gadolinium- based contrast became increasingly popular. The indications expanded from head and spine imaging to body applications, and then to pediatric examinations. Radiologists started looking into off-label indications as well. The moves in that direction started early, with researchers first playing with double and triple doses, then turning to MR angiography.

Time-of-flight and phase-contrast techniques without the use of a contrast agent had not proved better than x-ray techniques. The angiography contrast agents in the pipeline were not yet ready. So why not use the existing agents at a higher dose? Techniques were patented by MRA protagonists, and companies were easily persuaded to give a helping hand to the off-label application.

Warning voices were not heard. Gadolinium-based agents were believed to be risk-free. The physicians involved had no background in the complex mechanisms of the behavior and biochemistry of gadolinium contrast agents. Laboratory chemists and biologists did not understand the paths of medical thinking. Marketing staff were deeply ignorant, and those in R&D were too low down the pecking order to be asked.

Undue Diligence

Meanwhile, a big scare broke loose on a different front. A wave of company- sponsored satellite meetings flooded the free-lunch floors of scientific conferences, each bringing the message that only certain iodinated contrast agents should be used in patients with restricted kidney function. The entire move was more a marketing operation than anything based on scientific evidence. Its aim was most likely to prevent harmed patients from further harm. But the road to hell is plastered with good intentions.

Some people thought further. Others smelled money. Why not replace x-ray examinations in kidney patients with contrast-enhanced MR imaging? These examinations would involve no ionizing radiation and would use less aggressive contrast agents. Studies by radiologists performing MRA had shown that this practice was safe. They all focused upon nephrotoxicity, stating that high-dose gadolinium chelates were significantly less nephrotoxic than iodinated contrast agents [6].

To corroborate these results, a phase III clinical study was performed in a major university hospital. Several dozen people with renal failure were enrolled. The trial ended in disaster, though not immediately. At the end of the trial, everything looked positive [7]. As in the Thorotrast case, the damage became clear later, after weeks, months, years.

Many of the trial's participants developed strange symptoms. They were identified as having developed

nephrogenic systemic fibrosis, a systemic disorder characterized by thickening and tightening of the skin and subcutaneous tissues. NSF can include fibrosis of skeletal muscle, lung, liver, testes, or myocardium. The effects are irreversible–believed to be related to gadolinium freed into the body. It is an iatrogenic disease with a possibly fatal outcome [8].

NSF was originally known as nephrogenic fibrosing dermopathy owing to the typical initial symptoms of symmetric swelling, discoloration, and pain of the lower legs. The first case was described nine years after the introduction of Magnevist, four years after the introduction of Omniscan. The first major article describing 15 patients with NSF appeared in 2000 [9].

The accepted school of thought today is that gadolinium-based contrast agents administered in high doses have high nephrotoxicity [10]. The medical community also seems to have realized that free gadolinium may accumulate in tissues when contrast is administered in high doses or in repeated examinations to patients with severe kidney disease. The number of new NSF cases seems to be on the decline now that this information has been taken on board.

Two studies just published reported incidence of NSF between one in 2913 and one in 44,224 patients, depending on contrast agent, dose, frequency of injection, and severity of kidney disease [11, 12]. These figures make me wonder. Basically, these numbers don't say anything because the selected groups are not comparable. The rates are quite high, considering that only around 250 cases have been reported worldwide. These cases are accompanied by at least 500 more or less learned papers on the topic since 2000.

In the general patient population, the overall rate of incidence of NSF is probably one or two orders of magnitude lower, and the chance of an average patient being affected after undergoing contrast-enhanced MR imaging is negligible. The agents' diagnostic benefit is undisputed – if used properly, not in doubtful indications. Contrast agents are used for more than 50% of all MR imaging examinations in some countries. There is no medical reason for that.

Corporate (Ir-)Responsibility?

In the words of Dr. Peter Marckmann from the department of nephrology at Copenhagen University Hospital, "Unfortunately, there is no proven curative treatment. It is therefore essential that future cases of nephrogenic systemic fibrosis are prevented." [13]

There is an outrage among radiologists. At every minor or major radiological meeting, entire sessions are devoted to NSF, navigating between Scylla and Charybdis. Everybody is looking for explanations and somebody to blame.

So who or what is to blame? Greed is the most likely culprit. It is not only stupidity, "negligence," or "human error"– those unavoidable factors cited at news conferences: "Sorry, it happened – it was unpredictable, an accident." A friendly smile and back to today's agenda.

Frankly, the first to blame are those radiologists who used the drugs off-label. If you apply a drug outside the recommended and approved protocol, you bear the responsibility. It is as simple as that.

If you talk to fellow radiologists, you will soon discover that most do not know how these drugs function; "gado" is no "dye." There is a rather complicated mechanism behind these drugs' contrast altering actions. Furthermore, even the most mentally challenged physician knows that the pharmaceutical industry will not inform you about possible unpleasant characteristics of their products, particularly if they hope these characteristics will not show up if the drug is applied within the strict limits of its approved use.

But the fingers itch. Let's make more money even if there is a rotten smell: "Push the fresh fish."

I reckon that the main factor is ignorance and lack of ethics. Radiologists should know what they inject. This is something one does not necessarily learn at free-lunch or free-dinner meetings. If you pay for yourself and try to understand the boring background, then you buy peace of mind. It's you, the radiologist, who will have to face the patients afterwards.

And the companies? Those answerable have long moved on, gliding to new sinecures on a golden parachute.

By the way, two top managers at a multinational fish farming company used to be top managers at one of the contrast agent producers.

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