

# COMMENTARY

## Mobile phones and the illusory pursuit of safety

See pages 1833, 1837

Two papers in today's *Lancet* address the controversial subject of safety of mobile telephones. Ken Rothman considers the issue from an epidemiological viewpoint, whereas G J Hyland seeks a possible mechanism for harmful effects. Readers will make up their own minds, both on their own views and on what they should say to anxious patients. However, it is worthwhile rehearsing a few salient points.

The deceptively simple question, much loved by television and radio interviewers, "Is it safe?" is the scientist's banana skin. A Nobel prize awaits the person who first designs an experiment to show that anything is "safe". The best that can be achieved is an experiment or epidemiological analysis of data that demonstrates, within specified limits of statistical probability, that the risk associated with a drug, a new mode of radiation, or other insult to the body is no greater than a specified figure—for example, one in a million.

In the light of experience with ionising radiation and radioactive materials, out-of-hand dismissal of the possibility of subtle effects of low-intensity, pulsed, microwave radiation is most unwise. Early in the 20th century radon and radium-enriched spa waters were "recommended" for a wide range of aches and minor ailments.<sup>1,2</sup> As knowledge of the harmful effects of ionising radiation has increased and quantitative risk estimates have become possible (notwithstanding rather large error bands), the permitted annual dose limit has been progressively reduced from the 1930s to the present day.

Rothman concludes that it is too soon to reach a verdict on the health risks from cellular telephones. Hyland suggests that there may be subtle, non-thermal effects, principally associated with a synergy or resonance between the frequencies generated by various features of the mobile telephone process and natural body frequencies. How should one weigh the various reported effects, whether harmful or not, that Hyland cites?

Have the findings been reproducible? In many cases they have not. Hyland suggests that the highly non-linear nature of living systems militates against the realisation of the identical conditions for exact replication, but this argument confuses deterministic effects, which will always occur above a certain threshold of insult, and stochastic ones, which are governed by the laws of chance. Buying one ticket and winning the lottery is an excellent example of a stochastic effect. Biological systems are subject to the same laws, albeit with a higher level of noise.

Are the key experiments closely linked to the proposed mechanism? The postulate that exceptionally low intensities of microwave radiation can have a disproportionately high effect at certain frequencies implies that the effect should disappear when the

frequency is "off-resonance". Such experiments may be very difficult to design in vivo and do not seem to have been done.

Have anecdotal reports been followed up by other workers? By their nature such reports are very selective and, to gain credibility, must be corroborated by results from an experimental design in which potential bias has been eliminated. Some papers that did not corroborate earlier findings have been published, as Hyland notes.<sup>3</sup> Would a journal of negative results have published even more? On the other hand, I am aware of two epidemiological studies that have become the subject of legal scrutiny, resulting in curtailment or publication delay. Such intervention inevitably weakens the evidence base on which balanced views should be made. Hyland is right to call for further research but there needs to be a consensus about the most likely interaction mechanisms around which the experiments should be designed.

At present it is difficult to make a logical case for more stringent limits on exposure to pulsed microwave radiation. Robust limits are based on either a direct quantitative link between cause and effect (eg, thermal heating) or on a proven causative mechanism supported by dose-effect relations, as found with ionising radiation. Neither is available for these postulated very-low-intensity effects; the process of ionisation and free-radical formation that is known to be the basis of cancer induction with, say, X rays, does not occur with electromagnetic radiation in the microwave frequency range.

Ultimately the public perception of safety will be heavily influenced by the perceived level of benefit from the activity in question. This level is clearly high in the case of mobile telephones and in many other domains where individuals exercise freedom of choice. The title of this commentary draws on an editorial in the *Guardian* newspaper on the announcement, back in 1977, that there was to be an inquiry into a cluster of explosions of domestic gas. That editorial said: "Whatever the findings of the three-man enquiry (under an independent chairman) gas will not become safe. Some oaf will always leave a tap on and then go down at the dead of night with a lighted taper". This highly explosive substance is piped into millions of homes in the country. Is it safe? Of course not but the amenity value is such that people are prepared to live with the risk. Researchers into the pursuit of safety, of mobile telephones or other features of modern living, would be well advised to take this political element into consideration.

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- 1 Humphries FH, Williams L. *Emanotherapy*. London: Baillière, Tindal and Cox, 1937.
- 2 Mould RF. *A century of X-rays and radioactivity in medicine*. Bristol: Institute of Physics Publishing, 1993.
- 3 Malyapa RS, Ahern EW, Bi C, et al. DNA damage in rat brain cells after in vivo exposure to 2450 MHz electromagnetic radiation and various methods of euthanasia. *Radiation Res* 1998; **149**: 637-45

## Calprotectin, a faecal marker of organic gastrointestinal abnormality

Calprotectin, a 36 kDa calcium and zinc binding protein, constitutes about 60% of soluble cytosol proteins in human neutrophil granulocytes.<sup>1</sup> It was initially called leukocyte L1 protein, after being discovered in the search for a plasma marker of increased granulocyte turnover.<sup>2</sup> Its abundance in granulocytes and antimicrobial activity suggest that it has a central role in neutrophil defence.<sup>3</sup> Rat calprotectin can induce apoptosis in several human and murine tumour cell lines and, like the antimicrobial activity, this effect is blocked by zinc.<sup>4</sup> Calprotectin may therefore exert its effects by reducing local concentrations of zinc, which indicates that it may be involved in the regulation of inflammatory reactions by its inhibition of several zinc-dependent metalloproteinases. The protein is remarkably resistant to degradation in vivo and in vitro in the presence of calcium,<sup>5,6</sup> so faecal samples can be sent to the laboratory by post. The upper reference limit in faeces is 10 mg/L, but with a recent refinement of the assay, which does away with the messy step of homogenisation and which increases yields, the limit is 50 mg/L.<sup>7</sup>

Several groups have confirmed the observation<sup>5</sup> that calprotectin can be assayed in simple buffer extracts of small (5 g) faecal samples, and that increased concentrations (>10 mg/L) are found in most patients with inflammatory bowel disease (IBD) or gastric or colorectal cancer (panel). It was therefore quite clear at an early stage that the faecal calprotectin test was non-specific for type of organic bowel disease. In different studies the median values in patients with colorectal cancer ranged from 33 to 214 mg/L. In one study 23 patients were also tested after resection, and the median dropped from 75 to 9 mg/L.<sup>8</sup>

O Kronborg and colleagues<sup>15</sup> have recently investigated whether the calprotectin test can be used for screening symptom-free individuals for early neoplasia. They

concluded that, with its specificity of only 64% for no cancer and 67% for no neoplasia, it cannot, except for individuals in high-risk groups. In this study the median concentrations were 6.6 mg/L in the controls (n=488), 9.1 among patients with colorectal adenomas (n=203), and 13 among those with colorectal cancer (n=23). Concentrations in the neoplasia groups were thus much lower than in previous studies and probably reflect the early stages of the diseases. Sensitivities were 43% for adenomas and 74% for cancer, whereas other studies showed a sensitivity of about 92% in patients with colorectal cancer.<sup>8,10</sup> The patients in these other studies were tested while awaiting endoscopy, and all patients referred for endoscopy were included—ie, there was no selection by, for instance, severity or type of symptoms. Nevertheless, for a screening test, specificity must also be adequate.

Very different types of abnormality can give a positive faecal calprotectin test: neoplasia, IBD, infections, and the use of non-steroidal anti-inflammatory drugs.<sup>16,17</sup> Generally, defects or increased permeability of the mucosal barrier will cause migration of large numbers of granulocytes into the intestinal lumen as a chemotactic response to the enormous number of bacteria in the bowel. By contrast, gastrointestinal bleeding of as much as 100 mL daily would be needed to increase the faecal calprotectin concentration by 6 mg/L.<sup>8</sup> When mucosal lesions are extensive, for instance as in IBD, calprotectin concentrations are generally ten to 20 times the upper reference limit; the “unofficial world record” is 40 000 mg/L in a patient with active Crohn’s disease at Aker Hospital in Oslo. The great variation in reported values in IBD (panel) is probably due to there being only a small proportion of the patients with clinical relapses. Faecal calprotectin predicts clinical relapse of IBD,<sup>17</sup> a finding in keeping with the correlations between excretion of indium-111-labelled autologous granulocytes ( $r=0.8$ ;  $p<0.0001$ )<sup>14</sup> and histological grading ( $r=0.62$ ;  $p<0.001$ ).<sup>12</sup> Another recent study<sup>18</sup> has suggested that calprotectin may help in discriminating between patients with Crohn’s disease and irritable-bowel syndrome. As an objective variable suitable for sequential measurements, it has the potential to be used for monitoring the efficacy of new therapeutic regimens for IBD—for instance, infusion of monoclonal antibodies against tumour necrosis factor, which is activated by a zinc-dependent metalloproteinase. It might also be used to test for gastrointestinal side-effects of new nonsteroidal anti-inflammatory drugs.

In general medical practice there is a need for a simple test to assist in the selection of patients with prolonged diarrhoea and/or other non-specific gastrointestinal symptoms for complex diagnostic procedures, especially among children, who may require general anaesthesia for endoscopy. Calprotectin could be a candidate for this purpose since a cutoff at 30 mg/L had 100% sensitivity in discriminating between active Crohn’s disease and irritable-colon syndrome.<sup>18</sup>

I share patent rights on calprotectin.

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- 2 Fagerhol MK, Dale I, Andersson T. Release and quantitation of a leucocyte derived protein (L1). *Scand J Haematol* 1980; **24**: 393-98.

### Faecal calprotectin concentrations in patients with colorectal cancer or inflammatory bowel disease\*

References	Calprotectin concentration (mg/L)		
	n	Median	Range
<b>Colorectal cancer</b>			
Røseth et al <sup>5</sup>	11	40	6-80
Røseth et al <sup>8</sup>	53	50	4-300
Kristinsson et al <sup>9</sup>	119	50	2-950
Campbell et al <sup>10</sup>	11	214	49-410
Gilbert et al <sup>11</sup>	14	33	4-382
<b>Inflammatory bowel disease</b>			
Røseth et al <sup>5</sup>	38	42	4-1800
Røseth et al <sup>12</sup>	29	132	5-5847
Campbell et al <sup>10</sup>	36	216	1-1376
Røseth et al <sup>13</sup>	62	68	11-170
Tibble et al <sup>14</sup>	80	78	28-142

\*Upper reference limit 10 mg/L.