proteins performing the same function in hibernating animals (UCP1).[3] The second source comes from yeast experiments.[3] In these the UCP2 gene was expressed in yeast mitochondria and the electrical potential across the mitochondria was observed to go down. This drop in electrical potential suggests that a proton leak—and hence uncoupling—is occurring. In addition, when the modified mitochondria were purified they were shown to be less well coupled, producing more heat and less useful energy, compared with wild type yeast cells.

Although these proteins have been quickly named uncoupling proteins—implying that their function has been well worked out—this is not the case, and several arguments exist against these proteins having a specific uncoupling function. In the yeast experiments, for example, uncoupling may have occurred simply because the yeast mitochondrial membrane had been destabilised by an alien protein. And in a set of experiments on the muscles of hungry rats, where uncoupling protein content was predicted to go down, it actually went up.[4] In general, expression of uncoupling protein mRNA seems to correlate better with fatty acid metabolism than with metabolic efficiency.

The most conclusive way to confirm the function of uncoupling proteins is to produce genetically engineered mice in which the genes that encode the proteins are either knocked out altogether or overexpressed. If this results in mice which are obese in the first case or skinny in the second then these proteins stand to be good targets for antiobesity drugs. The aim then will be to find agents which can turn up the uncoupling activity enough to cause weight loss.

Both leptin manipulation and uncoupling proteins are fuelling excitement among drug companies. The greatest promise may come from a combination of drugs that fool the brain into thinking we're fatter than we are (such as leptin, which reduces the appetite and increases energy burn) and those which turn up energy expenditure to help burn off those calories already there or about to be eaten (increasing uncoupling protein activity).

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Emotional wellbeing and its relation to health

Physical disease may well result from emotional distress

In 1947 the World Health Organisation defined health as "a state of complete physical, mental and social wellbeing."[1] Until now the NHS has given precedence to promoting physical wellbeing, but the green paper *Our Healthier Nation* signals that this may need to change.[2] It emphasises the importance of emotional wellbeing for health: indeed, health is defined as "being confident and positive and able to cope with the ups and downs of life." These statements are supported by an increasing body of epidemiological, social science, and experimental research that is beginning to suggest that initiatives which aim to promote physical wellbeing to the exclusion of mental and social wellbeing may be doomed to failure.

The concept of mental and social wellbeing is less well defined than that of physical wellbeing. Debate still continues about the meaning of the term mental health. A recent study in Scotland showed that lay people were more comfortable with the terms psychological and emotional wellbeing because they equated the term mental health with mental illness.[3] The concepts of social wellbeing and social disease (misuse of alcohol and drugs, domestic violence, child abuse) and the extent to which they are the responsibility of the NHS is also controversial.

Nevertheless, some research shows that emotional distress creates susceptibility to physical illness. Exam stress increases susceptibility to viral infection,[4] and stress from lack of control in the workplace[5] or from life events[6] creates susceptibility to cardiovascular disease. Animal studies reviewed by Wilkinson[7] and Brunner[8] provide supporting evidence that emotional distress can lead to physical illness by affecting the immune response. Health related lifestyles provide the basis for an alternative, potentially complementary, causal hypothesis. Smoking, drinking, and the consumption of high fat foods are all valued by the public for their ability to relieve emotional distress.[9] Collectively these studies are beginning to lend credence to the widespread public belief that physical disease may be the consequence of emotional distress.

Several epidemiological studies have shown that social and emotional support can protect against premature mortality, prevent illness, and aid recovery.[10 11] It is plausible that these could act by reducing emotional distress. Various different types of study have suggested that as important for health as income differentials is social capital—that is, features of social organisation (civic participation, social trust) that facilitate cooperation for mutual benefit.[7] One of these studies examined the relation between income differentials and responses to the question "Do you think that most people would try to take advantage of you if they got the chance?" in a representative survey.[12] The collective response of communities to these questions predicted age adjusted mortality rates better than

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the Robin Hood index, a well validated measure of income differentials. Income differentials vary over time and from place to place,[7] suggesting that they are not just a fact of life. It could be argued that wide income differentials are an economic manifestation of people taking advantage of each other, and that it is the latter that causes premature mortality—through the emotional distress it generates.

Solutions to apparently intractable public health problems like inequalities in health and unhealthy lifestyles may therefore lie in research into emotional wellbeing. A broad range of studies is needed to test the hypothesis that emotional distress creates susceptibility to physical illness and a further range is to research interventions which can prevent emotional distress and promote mental and social health.

Two of the most promising approaches depend on a further body of research which shows that unresolved emotional distress in childhood is an important cause of emotional distress in adulthood.[13 14] These approaches are parenting programmes and mental health promotion programmes in schools. The evidence showing that parenting programmes can both reverse emotional and behavioural problems[15] and prevent their emergence[16] is robust. Several school mental health promotion programmes have been subject to controlled trials which show a positive impact on emotional wellbeing.[17] Through developing empathy and respect, both types of programmes improve self esteem in children and parents and increase their ability to give and receive social and emotional support. Long term follow up studies are needed to test the hypothesis that these programmes affect adult physical and mental health, but the epidemiological evidence suggesting that they could is strong.

Successful implementation of the agenda defined in *Our Healthier Nation* will depend on research and development of such programmes. For this to happen doctors, and others who determine the allocation of NHS funds, will need to believe that emotional and social wellbeing are at least as important for health as physical wellbeing and invest both development and research funds accordingly.

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Paracetamol (acetaminophen) poisoning

No need to change current guidelines to accident departments

Letters p 1654

Paracetamol is an effective, simple analgesic that is well tolerated by adults and children at therapeutic doses. In many countries it is available without prescription. Unfortunately, its ready availability is associated with episodes of poisoning that prompt 3.3% of inquiries to US regional poisons centres,[1] 10% of inquiries to the UK National Poisons Information Service,[2] and up to 43% of all admissions to hospital with self poisoning in the United Kingdom.[3] In the United States paracetamol alone accounted for 4.1% of deaths from poisoning reported to American poisons centres in 1997.[1] Most deaths are associated with deliberate self poisoning, but therapeutic misadventures do occur rarely, in both adults and children.

In a recent lesson of the week Bridger et al, on the basis of four cases, advocated instigating treatment for paracetamol poisoning at levels below the normal "treatment line" of paracetamol concentrations at four and 15 hours advised in the current guidelines on paracetamol poisoning issued by the UK National Poisons Information Service.[4] This paper has generated considerable debate, which is reflected in this week's letters columns (p 1654).[5] Is it time to revise the guidelines?

The paper by Bridger et al was inappropriately entitled "Deaths from low dose paracetamol poisoning" because at least three of the four subjects ingested potentially hepatotoxic amounts ("150 mg/kg body weight or 12 g in total, whichever is the smaller"). Nevertheless, since there are effective antidotes in those who present relatively early after overdose, we are concerned about all possibly avoidable deaths due to paracetamol poisoning.

Paracetamol is predominantly metabolised to glucuronide and sulphate conjugates, which are excreted in the urine. Hepatotoxicity is related to the conversion of a small proportion of the ingested dose to N-acetyl-p-benzoquinoneimine. In therapeutic doses N-acetyl-p-benzoquinoneimine is detoxified by

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