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The health effects of oilseed rape: myth or reality?

No clear evidence that it has adverse effects on health

Oilseed rape (*Brassica napus*) has been cultivated without problems for centuries, and public suspicion that oilseed rape might have an adverse effect on health arose only when the acreage of this crop rapidly increased in the 1980s—and only in Britain. Responding to this concern, the British Medical Research Council's Institute of Environment and Health examined the problem at an experts' meeting in 1996 and has recently published an annotated review on the allergenicity and irritancy of oilseed rape.[1] Although not drawing final conclusions, this report may help both the practising doctor and the scientist by providing clearcut statements on what we do and don't know. Essentially the report shows that there is evidence of health effects associated with the cultivation of oilseed rape but no convincing evidence that rape is a cause of widespread disease or ill health in the general population.

Several studies show that pollen from oilseed rape is allergenic,[2-6] but data on the incidence of sensitisation are highly conflicting. High figures reported in two early studies[2 3] probably rest on oversensitive techniques of inadequate specificity. They appear doubtful in the light of subsequent studies,[4-6] which agree that allergy to rape pollen is uncommon, even in areas of intense cultivation. Furthermore, sensitisation is largely confined to people with atopy with multiple sensitivities. There is poor evidence that oilseed rape pollen itself actively sensitises—except perhaps for occupational exposure[5]—which is reflected in the scarcity of monosensitised subjects. Our recent findings on oilseed rape allergens indicate broad cross reactivity with birch and grass pollen allergens, involving profilin, calcium binding proteins, and other so far unidentified proteins, and make us speculate that the oilseed rape allergic pool is mainly a subset of grass pollen allergic patients recognising cross-reacting epitopes in oilseed rape.[7] These patients may experience allergic symptoms when exposed to rape pollen and, considering cross-reactivities, oilseed rape might protract or augment symptoms in leaf tree and grass pollinosis.

Studies on the dispersal of oilseed rape pollen generally conclude that, although more than 1000 grains/m^3 can be trapped in or at the edges of the fields, very little airborne pollen is transported over longer distances.[8 9] Maximum pollen levels near human dwellings as measured during clinical studies were around 100 grains/m^3/24 h, a load possibly enough to provoke an allergic reaction, but such high values were achieved only on a few days of the pollen season.[5 6 10] Hence, sensitisation does occur but mainly affects people with atopy and will be clinically relevant only during peak flowering days or in close proximity to fields.

Standardised rape pollen extracts are required for future investigations to obtain more reliable results, but much higher prevalances of allergy are unlikely to be obtained using such improved extracts. Consequently, researchers have looked for other mechanisms that could explain the adverse effects attributed to the cultivation of oilseed rape. Pesticides have been blamed. Experts agree, however, that no substantial basis exists for this assumption since the range of agrochemicals used in rape cultivation does not differ from that of other crops. Others have suggested the involvement of mould allergy[10] as the crop is commonly infested with fungi during seed ripening. Although high loads of airborne mould spores have been found near fields there is no empirical to substantiate this idea.

When it became clear that pollen allergy was unlikely to be the key factor in adverse effects associated with oilseed rape, attention switched to the possible irritant effects of volatile organic compounds emitted by the plant. Some of the volatile chemicals detected in oilseed rape,[11] such as terpenes, aldehydes, organic disulphides, and, in macerated plants, isothiocyanates, may theoretically account for adverse effects through by their irritant action on mucous membranes. On the other hand, we do not know whether these compounds in nature ever reach concentrations high enough to elicit physiological effects: if they did so they would have to be in concentrations at least several orders of magnitude above the level at which they could be detected by smell. Clinical data from population studies on the possible effects of volatile organic compounds is scarce. Higher prevalences of headaches, cough, and wheezing—at the borderlines of statistical significance—have been described from areas of oilseed rape cultivation,[10 12] but symptom scores were generally low in these studies and no correction was made for other potential factors, such as climate, that might have explained the observed differences. Hence, the role of these compounds remains speculative, though further studies seem to be justified.

Only in Britain has oilseed rape been suspected by the public of causing ill health effects. In other rape growing countries, such as France, Germany, Denmark, and Canada, no such public concern against oilseed rape exists. Is there some prejudice because the expansion of this crop is subsidised by the European Union,

or do people simply dislike its intense smell and flashy yellow flowers? Science must never ignore potential health hazards, but so far there is little evidence to incriminate a versatile crop of economic importance as a cause of ill health.

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Endothelial cell activation

A central pathophysiological process

The endothelium is now recognised as not simply being an inert lining to blood vessels, as thought in the 1960s, but a highly specialised, metabolically active interface between blood and the underlying tissues—maintaining vascular tone, thromboresistance, and a selective permeability to cells and proteins. Moreover, under the stimulation of agents such as interleukin 1, the endothelium undergoes changes which allow it to participate in the inflammatory response; this is known as endothelial cell activation.

The term was coined in the 1960s by Willms-Kretschmer.[1] He noted that in delayed hypersensitivity reactions the endothelium became plump and leaky and displayed increased quantities of biosynthetic organelles such as endoplasmic reticulum.[1] He used the term activated to imply a change in function as well as morphology. In the 1980s an avalanche of papers showed that the newly discovered cytokines, interleukin 1 and tumour necrosis factor, changed surface molecules and thus the functions of cultured endothelial cells. To emphasise that these changes did not represent injury or dysfunction, Pober reintroduced the term endothelial cell activation.[2]

Activation entails a stereotyped series of processes, although their effects are diverse and are seen differently by specialists in different disciplines. Immunologists study upregulation of surface antigens and adhesion molecules, while those in thrombosis research assess prothrombotic endothelial cell changes, and vascular biologists study changes in tone. All these effects, however, are components of endothelial cell activation and mutually interact in causing local inflammation.

The five core changes of endothelial cell activation are loss of vascular integrity; expression of leucocyte adhesion molecules; change in phenotype from antithrombotic to prothrombotic; cytokine production; and upregulation of HLA molecules.

Loss of vascular integrity can expose subendothelium and cause the efflux of fluids from the intravascular space. Upregulation of leucocyte adhesion molecules such as E-selectin, ICAM-1, and VCAM-1 allows leucocytes to adhere to endothelium and then move into the tissues.[3] The prothrombotic effects of endothelial cell activation include loss of the surface anticoagulant molecules thrombomodulin and heparan sulphate; reduced fibrinolytic potential due to enhanced plasminogen activator inhibitor type 1 release; loss of the platelet antiaggregatory effects of ecto-ADPases and prostacyclin; and production of platelet activating factor, nitric oxide, and expression of tissue factor.[4] Cytokines are synthesised, including interleukin 6, which regulates the acute phase response, and chemoattractants such as interleukin 8 and monocyte chemoattractant protein 1.[5] Expression of class II HLA molecules allows endothelial cells to act as antigen presenting cells, especially important in transplant rejection.[6]

Two stages of endothelial cell activation exist[4]; the first, endothelial cell stimulation or endothelial cell activation type I, does not require de novo protein synthesis or gene upregulation and occurs rapidly. Effects include the retraction of endothelial cells, expression of P selectin, and release of von Willebrand factor. The second response, endothelial cell activation type II, requires time for the stimulating agent to cause an effect via gene transcription and protein synthesis. The genes involved are those for adhesion molecules, cytokines, and tissue factor.

Our growing understanding of intracellular signalling has led to the discovery that the diverse effects of endothelial cell activation share a common intracellular control mechanism through the activation of the transcription factors, including nuclear factor κB.[7] A stimulating agent acting at the endothelial cell surface causes the activation of cytoplasmic nuclear factor κB. Once activated, nuclear factor κB is transported into the nucleus and binds to promoter areas of genes which are upregulated in endothelial cell activation.

So what do we gain from understanding endothelial cell activation? It seems to be a common pathogenic mechanism for it is induced by a wide range of agents such as certain bacteria and viruses, interleukin 1 and tumour necrosis factor, physical and oxidative stress, oxidised low density lipoproteins,[8] and antiendothelial cell antibodies (found in systemic

autoimmune diseases such as the vasculitides, systemic lupus erythematosis, and antiphospholipid syndrome[9]). Endothelial cell activation is a graded rather than an all or nothing response—for example, changes in endothelial cell integrity range from simple increases in local permeability to major endothelial cell contraction, exposing large areas of subendothelium. Activation may occur locally, as in transplant rejection,[4] or systemically, as in septicaemia and the systemic inflammatory response. In atherosclerosis endothelial cell activation may mediate the deposition of atheroma for oxidised low density lipoprotein causes endothelial cell activation. In vitro advanced glycation end products mediate prolonged activation of nuclear factor κB, thus tantalisingly suggesting that vascular diabetic complications may be due to chronic endothelial cell activation.[10] The picture is incomplete as yet, for some mechanisms of endothelial cell activation have been observed only in vitro or in animals.

The discovery of the intracellular mechanisms of endothelial cell activation have thrown light on how some long established treatments work. Some of the antiinflammatory effects of glucocorticoids[11] and aspirin[12] act through inhibition of nuclear factor κB. As a transcriptional activator of the genes of endothelial cell activation, nucear factor κB itself is an interesting target for pharmacological manipulation, and fundamental approaches to switching it off are being explored. This may provide novel therapeutic avenues for inflammatory conditions.

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Models of cardiac rehabilitation

Multidisciplinary rehabilitation is worthwhile, but how is it best delivered?

The survey by Lewin and colleagues of cardiac rehabilitation in the United Kingdom paints a picture of services predominantly provided by nurses and physiotherapists, with little formal input from physicians or psychologists, and a need both for more extensive use of validated methods of assessment and of formal audit (p 1354).[1] Clinicians will bristle (I bristled) at the insinuation that they are not involved in rehabilitation. Cardiac and general medical outpatients clinics are full, we say, of patients being followed up after myocardial infarction or cardiac surgery. In theory (our theory) this should run parallel with and form part of the formal rehabilitation process. In practice, it often does not. Ten minutes of structured consultant time in the context of a rehabilitation process may be more valuable and more cost effective than an isolated 10 minutes in the middle of a busy outpatient clinic. Reorganisation to implement this would be feasible, but care would be needed to preserve valuable features such as continuity of care.

The issue of psychological input is more difficult. There is good evidence that psychological morbidity, particularly depressive illness, is common after infarction.[2] However, intervention intended to counteract it has sometimes had paradoxical results and should certainly not be divorced from other rehabilitation measures.[3] Given a relative shortage of clinical psychologists, the best strategy is probably to use a well validated assessment instrument to identify patients at risk and to concentrate resources on them.

An important issue which is not addressed in the survey is the extent to which cardiac rehabilitation should be hospital or community based. Rehabilitation guidelines rightly emphasise the need for a seamless rehabilitation service extending from acute hospital care into long term community follow up.[4] However, few services have been successfully developed which actually provide this, and the idea sits uneasily with traditional ideas about the scope of secondary and primary care, or divisions between purchaser and provider. The concept of a rehabilitation cardiologist, from either a hospital or primary care background, who could provide a bridge between hospital and community rehabilitation is an attractive one, but is largely unproved. To what extent is it legitimate to separate cardiac rehabilitation from rehabilitation services in general? In many hospitals cardiac rehabilitation has evolved in isolation from rehabilitation linked to other specialist services, or from general rehabilitation aimed at the elderly. In our hospital the median age for cardiac surgery is now 65, and such traditional distinctions may need to be rethought.

The survey also mentions resources. Until relatively recently the inability of clinical trials of exercise based cardiac rehabilitation programmes to show benefit in terms of survival put them at a disadvantage in competing for resources in a cash limited health service. There is now recognition that cardiac rehabilitation in a wider sense—encompassing secondary prevention and other multdisciplinary interventions—is worthwhile. But the deferred and sometimes unspectacular nature of its benefits mean that it inevitably loses out to more urgent imperatives such as acute admissions and dealing with waiting lists—a problem not limited to cardiac rehabilitation.[5] There is a temptation to set up token services whose inadequacies are cconcealed until they are properly audited.

The recognition in *Our Healthier Nation* of the importance of prevention and rehabilitation is welcome,[6] but it remains to be seen whether this is backed up by resources. The shift of emphasis from general practitioner fundholding to community commissioning may provide a unique opportunity to set up integrated rehabilitation services. In addition, a greater emphasis on return to work should encourage links with occupational health services. Meanwhile, the onus is on the rehabilitation community to come up with clinically and economically effective models from which to deliver optimal rehabilitation.

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Lithium

Still effective despite its detractors

In 1812 Benjamin Rush observed that "Many mad people, who have attempted to destroy themselves by cutting their throats . . . have been cured by the profuse haemorrhages." Blood letting soon became his first remedy for mania.[1] With the advent of a more scientific approach to medicine, this treatment, based on centuries of tradition and glowing clinical testimonials, fell into well deserved disrepute. Should lithium follow it?

Almost 140 years after Rush's observations John Cade noted that the toxicity of urine injected into guinea pigs was attenuated by lithium. After finding that lithium had "no discernable ill effects" when he took it himself, Cade successfully treated 10 manic patients with the drug.[2] Thus, in 1949, the modern era of lithium therapy began. Almost simultaneously, however, the ill advised use of lithium chloride as a salt substitute for patients on low sodium diets produced reports of neurotoxicity and death.[3] From this beginning the battle lines were drawn. Was this simple element a safe and effective cure for various ills or an ineffective but toxic nostrum?

In 1968 Blackwell and Shepherd suggested that lithium prophylaxis for bipolar disorder was "another therapeutic myth"[4]—the mid-20th century equivalent of blood letting. Subsequently several placebo controlled trials proved successful and the critics were silenced—but only temporarily. Recently, after reconsidering the "evidence," Moncrieff concluded that lithium may be ineffective not only for prophylaxis but also for acute mania and for augmentation in treatment resistant depression.[5] Her assertions have not gone unchallenged[7] and, in general, lithium remains a highly valued treatment modality.[8]

The early double blind, placebo controlled studies of lithium for acute mania were less than ideal in design, but, despite the drawbacks (which probably minimised the differences between lithium and placebo), lithium consistently outperformed placebo. Not until recently, however, was the antimanic efficacy of lithium confirmed in a large (n=179), multicentre, parallel design, placebo controlled study.[9] The impact of rescue medication was minimised by limiting it to chloral hydrate or lorazepam during the first 10 days of the three week study and never within eight hours of behavioural assessment. Based on an intention to treat analysis, 50% or greater improvement occurred in 49% of patients on lithium (n=36), 48% on divalproex (n=69), and 25% on placebo (n=74). Prior lithium treatment had been ineffective in 42% of those randomised to lithium, so the the deck was stacked against a favourable response to lithium, yet it emerged clearly superior to placebo. Nevertheless, in clinical practice few would argue that lithium alone is an adequate treatment for other than the milder cases of mania.

While lithium maybe an imperfect long term treatment for bipolar disorder, it is difficult to embrace Moncrieff's conclusion that it is ineffective. The abrupt withdrawal of lithium in placebo controlled discontinuation studies may have exaggerated drug-placebo differences because of withdrawal induced mania. Subsequent comparisons of affective morbidity with rapid (1-14 day) versus gradual (15-31 day) lithium discontinuation found more rapid and higher recurrence rates in the former group.[10] To use these observations to argue for the ineffectiveness of lithium prophylaxis is specious, however, because even with gradual discontinuation recurrence rates were high.

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When Goodwin and Jamison reviewed 10 placebo controlled maintenance studies, they found a relapse rate difference of 47% in favour of lithium.[11] A meta-analysis of placebo controlled studies found a 55% difference in relapse rate favouring lithium which reached a statistical significance of $p < 10^{-29}$.[12] There is growing, although not incontrovertible, evidence that lithium prophylaxis reduces mortality in patients with bipolar disease (particularly from suicide).[13]

Poorer responses to lithium have been associated with mixed or dysphoric mania, rapid cycling, many previous episodes, impaired functioning between episodes, and a depression-mania-euthymia course. While anticonvulsants such as carbamazepine and valproate (and more recently gabapentin and lamotrigine) show promise in these areas, properly designed studies have not compared their efficacy with lithium. At present alternatives to lithium are welcome options when lithium is ineffective or not tolerated, but it is questionable whether they should displace lithium as treatments of first choice.

The addition of lithium to an antidepressant to overcome treatment resistant depression has become an established intervention with about 50% effectiveness. Controlled studies continue to support this approach.[14 15] It is difficult to share Moncrieff's scepticism, especially when studies she reported as negative actually had positive outcomes.[15 16]

All drugs have side effects, and lithium is no exception. In overdose it is toxic, and deaths and permanent neurological and renal damage have occurred. Even at therapeutic levels, lithium commonly causes polyuria and impaired renal concentrating ability, and there is growing evidence that a minority of patients experience a gradual reduction in glomerular filtration rate which is probably caused by lithium.[17] Thus, periodic measurement of serum creatinine and, when indicated, 24 hour urine volume, protein, and creatinine clearance have become an integral part of long term lithium management.

Lithium is neither a paragon of therapeutic perfection nor a highly toxic placebo. Rather, it has established clinical utility for acute mania, for prophylaxis of bipolar (and probably unipolar) disorder, and for augmentation in treatment resistant depression. While we should continue to seek more effective and safer treatments, until they arrive the words of Ambroise Paré remain pertinent: "Better a tried remedy than a new fangled one."[18]

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Maintaining privacy and the health of the public

Should not be seen as in opposition

By a twist of irony one of America's foremost resources of clinical and epidemiological research has been struck by a growing concern about patient privacy.[1] Since the early 1900s the Mayo Clinic Foundation at Rochester, Minnesota, has maintained a medical record system that amounts to a population registry on health and disease.[2] Hundreds of clinical, biochemical, and epidemiological research papers have used old records and added new analyses or follow up data. Recent legislation in the state of Minnesota has made such use next to illegal. Minnesota is not the only place where privacy legislation is jeopardising the use of patient data for research. It is time to reassess the terms of the privacy debate.

In response to the Minnesota law the *New England Journal of Medicine* has devoted no fewer than four pages to a cry from the heart from Rochester.[1] The Mayo Clinic Foundation is setting up a heroic effort to obtain "broad informed consent" from all patients for future use of their data. Predictably, this will fall short of the requirements of those who demand specific informed consent for each piece of research—even retrospectively.[3] The mere possibility of litigation recently prevented the description of an epidemic of drug resistant tuberculosis by the Centers for Disease Control.[4]

How is the European situation evolving? Several years ago strongly worded editorials warned against a forthcoming European Community directive that, if

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applied literally, would have banned observational clinical and epidemiological research using old data from the old world.[5–7] Through a great lobbying effort by leading clinicians and epidemiologists the greatest danger was averted. The directive now has a clause permitting each member state to make exceptions for (public) health research. Is that progress? In the country I know best, the Netherlands, it seems not.

A document from the Dutch Health Council stipulates that informed consent is necessary even for completely anonymised record linkage. Strict laws regulating the privacy of patient-doctor encounters have been passed. A health inspector responsible for monitoring adverse drug reactions voiced his concern that to protect the public he might have to break the law. Within Dutch hospitals, administrators have questioned whether giving names of patients to health authorities responsible for tuberculosis contact tracing (when patients have been in the same room as a patient with tuberculosis) is still permitted under the new privacy laws. The same laws encourage doctors to destroy records older than 10-15 years—even if the diagnosis was vital, such as cancer—thereby making long term follow up impossible. Restrictive laws on the secondary use of body material are being prepared.

Despite newspaper publicity and questions in parliament, the issue seemed to have withered away, and the attempts of the Dutch Epidemiological Society to discuss the very real benefits from using old data were ignored by ministerial departments. Privacy issues have strong political attraction: right and left meet in a common distrust of big government and corporate medicine, and to promote autonomy. Quite recently, however, the Dutch Health Council chaired a (closed) meeting to assess the situation: it became clear that to steer and improve health care, authorities need linked information about healthcare processes—that is, about patients. Opinion remained divided whether some of the recent laws should be revised or whether the exceptions might be interpreted more liberally—for example, in cases where it is physically impossible to seek informed consent, where patients may be harmed by being told about a quite hypothetical hazard, or through the use of intermediate parties to anonymise the data but allow information to be traced back if necessary.

Medical journals are sensitive to the same fashionable pressures as politicians. Some (including the *BMJ*) have taken extreme views on informed consent in the rare case of publication of material that might identify a patient. In a recent debate in *JAMA* the public health community convincingly argued that overly restrictive positions might prevent important health information being disclosed any more: a consensus seems to be emerging that some balance needs to be restored.[4–9]

Pharmacoepidemiologists have been concerned with this issue for years. They study the effects and side effects of drugs by coupling existing data on treatments with records of disease. In a recent paper the International Society for Pharmaco-Epidemiology reiterated several often forgotten points.[10 11] Firstly, pharmacoepidemiological reports almost never identify individual patients: typically, they report rates and proportions in groups. Secondly, high quality research requires that the responsible researchers can go back to individual records: existing safeguards for discouraging the spread of information about individual patients by these researchers or their staff have sufficed. Finally, for completely anonymised record linkage no informed consent should be necessary.

A basic difficulty is that all parties too readily adopt an adversarial model which puts individual rights in opposition to public protection. The classic example is infectious disease, where freedom of movement for an individual can be curtailed for the greater good. Is the same opposition also true for the use of past records and material? The typical reaction of the lawyer or administrator who argues against the misuse of stored information, and therefore emphasises the need for privacy, is that "everyone agrees with the principle, and then asks for exceptions for themselves."

Perhaps we should stop the exceptions game. An important clarification came from the US Health and Human Services Secretary, Donna Shalala, who said: "We will recommend that a hospital be able to use personal health information to teach, train, conduct research, provide care, and ensure quality. But, on the other hand, employers who get health information to pay claims cannot use it for any non-health purposes, like hiring, firing, and promotions."[12] This makes the right distinction. Medicine evolves thanks to continuous learning from past mistakes and successes. The use of stored medical records, images, or body material should not be a matter of exceptions but should be seen as a monitoring task that is as necessary as individual patient care: neither can exist without the other. Given proper safeguards to protect the real interests of patients, society should understand that learning from the past is a task that has to be promoted positively, rather than a doubtful activity that has to jump ropes between litigation and legalistic loopholes.

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