to take place in more than one area" and "committees should arrive at a voluntary arrangement under which one LREC is nominated to consider the issue on behalf of all of them." If a tidy administrative solution is sought—and it is questionable whether that should have precedence over local autonomy—it is surprising that no mention is made of the possible role of a national research ethics committee in authorising multicentre studies conducted under the auspices of, for example, the Medical Research Council or Cancer Research Campaign.

The guidelines will also produce other frustrations for those planning multicentre studies. Some committees have their own application forms which must be completed and returned together with the protocol under consideration. Inevitably, these forms have not been standardised, with the result that many different forms may be required for the same study. The department should produce standard application forms for all proposed research projects, especially as this would also help maintain the register of proposed research which all ethics committees must now keep.

Lack of attention to practical detail is seen throughout the guidelines which, despite an assertion to the contrary in the accompanying circular, also fail to consider ethical principles governing the conduct of research. Perhaps it was never the department's intention to provide such a discussion. For whatever reason, those who serve on committees will have to seek ethical guidance elsewhere.

Implementation

District health authorities should have established committees operating in accordance with the guidelines by 1 February 1992. Many existing committees may assume that they have been operating largely within the spirit of the guidelines and that any changes in their procedures will be minimal. But this assumption ignores the new requirement that it is only the responsible NHS body which can approve a research proposal and that the committee's role is to offer independent advice on ethical issues. There is, however, a good argument for more public discussion of the costs and priorities in medical research. The old system of committees approving research purely on the basis of ethics was entirely ineffective in this respect, but the new arrangements place no obligation on the district health authority or other NHS bodies to discuss the issues in public. Ironically, the guidelines require an annual report from the committee in its advisory role but envisage no form of public report from the body that will actually decide whether research proposals will go ahead.

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(Accepted 11 February 1992)

For Debate

Psychological influences on cancer and ischaemic heart disease

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BMJ 1992;**304**:1295-8

For over a decade two academic psychologists, Professor H J Eysenck and Professor R Grossarth-Maticek, have reported a programme of research on the cause, prevention, and treatment of fatal diseases. Their main hypotheses are that particular personality traits increase the incidence of cancers and vascular diseases and that unhealthy personalities can be altered by psychological therapies, with a consequent reduction in death rates.

Unfortunately, descriptions of their methods, analyses, and results have been patchy and scattered widely in conference proceedings or in obscure or unrefereed journals and books.[1-6] Now, however, Eysenck and Grossarth-Maticek have published more detailed accounts in the widely read journal *Behaviour Research and Therapy*.[7,8] These long awaited papers contain some of the most remarkable claims ever to appear in a refereed scientific journal and it is difficult for anyone interested in the influence of psychological factors on physical illnesses to continue to ignore this work.

The investigations

The papers are based mainly on three aetiological investigations and several intervention studies. The first was an epidemiological study in the town of Crvenka in Yugoslavia. In 1965 a total of 1353 people were recruited, consisting of the oldest persons in randomly selected households plus 345 people who were considered "at high psychosomatic risk," the definition of which was "based on chronic hopelessness due to withdrawing objects or chronic anger due to disturbing objects."[9] Almost all subjects were aged between 48 and 68 years[5]; 71% were male, apparently because of selection of the oldest member of each household, although a later paper explained that the sex ratio was due to "the cultural preponderance of males, which for the sake of a good atmosphere for investigation, we did not try to overcome."[10] Onset of serious illnesses and causes of death were determined over the next 11 years. This follow up was 100% successful.[4]

In another study a random sample of 1026 people, mostly aged 40-60 years, was investigated in Heidelberg, Germany, between 1972 and 1982. Participants were asked to nominate friends and relatives who were "highly stressed," and these 1537 subjects, mainly aged 42-63 years, became the sample for a third cohort study.[5]

The investigators selected individuals from these and other Heidelberg surveys who were, in their view, at particular risk of developing either neoplastic or vascular diseases and randomly allocated them to preventive psychological interventions with follow up over the next seven to 13 years.[8] The various

preventive measures will be described in detail below.

As well as attempting to prevent cancer and vascular disease in those at high risk, Eysenck and Grossarth-Maticek conducted randomised trials of psychotherapy in 48 patients with inoperable carcinomas and 100 women with metastatic breast cancer.[8]

Yet another investigation, a cohort study of 7000 Heidelberg residents, has been briefly described in recent papers.[8 11] A subsample of 1863 subjects, mostly with the unhealthy personality types, was identified from within this large survey and the hypothesis that psychoanalytic psychotherapy can increase rates of fatal diseases was tested.

Personality types

The Eysenck and Grossarth-Maticek classification of unhealthy personalities developed from theoretical notions of the effects of emotional repression and also from early clinical observations.[12 13] It differentiates four types relevant to the development of serious physical illness. A "cancer prone personality" (type 1), characterised by "understimulation," was present in 28% of subjects in the large community surveys. About 25% showed a "coronary heart disease prone personality" (type 2), in which there is "a continued tendency to regard an emotionally highly important object as the most important cause for their particular distress and unhappiness." Another 15% of subjects were "a mixed type with psychopathic tendencies" (type 3). The "healthy, autonomous types" (type 4) comprised 29% of the subjects in the studies.

Some idea of the difficulties with definition and measurement of these categories can be obtained from the following decription of the cancer prone personality:

> Persons of this type show a permanent tendency to regard an emotionally highly valued object as the most important condition for their own well-being and happiness. The stress produced by the continued withdrawal or absence of this object is experienced as an emotionally traumatic event. Type 1 individuals fail to distance themselves from the object and remain dependent on it. Thus individuals of this type do not achieve success in reaching the object, and remain distant and isolated from this highly valued and emotionally important object. Great stress is produced by this failure to achieve nearness to the highly valued person, success in the highly valued occupation, or whatever. This type shows a lack of autonomy.[5]

A questionnaire has been developed to measure the personality types. Here are the first three items for type 1; all require yes/no responses.

> (1) Do you have a marked tendency to concern yourself lastingly with one emotionally important person, or one important aim in life, combined with a strongly marked faithfulness and a desire for belongingness?
> (2) Is it for you emotionally particularly important to achieve a lasting closeness and emotional attachment to a person who is important to you, but who has left you or is in the process of leaving you, or to achieve a very important aim which unfortunately is impossible for you to achieve?
> (3) After the departure of an emotionally important person, or the failure of an important aim, do you have feelings of inner emptiness, hopelessness, and depression, feelings which you try to hide from other people?[5]

Similar woolly definitions and clumsy questionnaire items are to be found for each of the personality types. The description of type 3 is another good example.

> Terms like "psychopath" and "personality disorder" readily spring to mind when looking at descriptions of the behaviour of "Type 3" individuals. In a recent study (unpublished) we have found a close relation between "Type 3" and sexual behaviour linked with Aids (large number of sexual partners, refusal to use condoms, homosexuality or bisexuality). . . . It seems likely that "Type 3" is related to Aids and other sexually transmitted diseases. . . .[5]

As yet, there have been no adequate published reliability and validity studies of the measurement of any of the categories, although a new, improved version of the inventory has undergone preliminary investigation as part of a 1974 study, not yet published, of no less than 19 000 subjects.[14]

In spite of all these problems, follow up after 10 years in the first three aetiological studies showed increased rates of neoplastic diseases and ischaemic heart disease in types 1 and 2 subjects which "remain highly significant even when smoking, cholesterol level and blood pressure are partialled out."[7] The authors, however, seem not to realise just what they are claiming. Out of 901 people with the cancer prone personality, 347 died of cancer, 61 died of ischaemic heart disease, and 155 of other causes. Of 818 with the coronary heart disease prone personality, 36 had died of cancer, 208 of ischaemic heart disease, and 221 of other causes. However, in the 946 subjects with the autonomous personality in the three studies, a total of 51 deaths had occurred after 10 years, of which only three were due to cancer and nine to ischaemic heart disease. This means that if we take the rates in the autonomous types as a baseline, Eysenck and Grossarth-Maticek have shown that type 2 subjects are 27 times more likely to die of ischaemic heart disease, and those with type 1 personality are 121 times more likely to die from a carcinoma. This relative risk of 121 is perhaps the highest ever identified in non-infectious disease epidemiology.

Prevention of cancer and vascular disease

These findings led on to attempts at prevention. Disease prone but otherwise healthy subjects were randomly assigned to a six month course of "creative novation behaviour therapy," a form of psychotherapy invented by Professor Grossarth-Maticek, who was the therapist in this trial.

After 13 years, 16 of 50 untreated type 1 subjects had died of a carcinoma. Not one of the 50 cancer prone subjects receiving the psychotherapy died of cancer. The therapy was a genuine panacea, giving equivalent results for type 2 subjects and heart disease. The all cause mortality was over 60% in untreated and 15% in treated subjects. The death rate in the untreated subjects was truly alarming as they began the trial healthy and most were between 40 and 60 years of age.

Following this success a randomised controlled trial of creative novation therapy, administered by Grossarth-Maticek as group therapy, was conducted in 490 people with the unhealthy personality types. The subjects were drawn from 3800 healthy but "highly stressed" respondents to a 1973 survey in Heidelberg. After seven years 20% of the treated group had died, compared with 76% of controls. Untreated subjects were six times more likely to die of cancer and three times more likely to die of ischaemic heart disease. Cancer was diagnosed in over half of the untreated subjects within the seven years of follow up, and these were particularly aggressive cancers: 85% of those who developed cancers died.

Both group and individual creative novation therapy are labour intensive. Therefore a randomised controlled trial of an explanatory pamphlet plus discussion of its contents ("bibliotherapy") was conducted on 1200 disease prone subjects. The leaflet had what the authors rightly call "a marked prophylactic effect" since 496 of 600 untreated controls (83%) are known to have died after 13 years, compared with 189 of 600 in the group who received bibliotherapy (32%).

The creative novation methods have been applied to treatment of neoplastic disorders as well as to their prevention. Twenty four pairs of "terminal cancer patients," individually matched for type of cancer,

progress of cancer, type of treatment, age, and sex, were identified and a member of each pair was randomly allocated to receive creative novation therapy from Professor Grossarth-Maticek. The mean survival time was five years in the treated group and three years in control subjects. Individual creative novation behaviour therapy had a similarly strong effect in prolonging the survival of women with metastatic breast cancer.

Eysenck and Grossarth-Maticek, therefore, are making claims which, if correct, would make creative novation therapy a vital part of public health policy throughout the world. But what is this therapy? The description in *Behaviour Research and Therapy* is a vague account of fairly routine behaviour therapy plus relaxation and a cognitive component. "Bibliotherapy" is decribed more precisely. It is given as a list of eight questions and answers, which were supplemented in the trial with three to five hours of discussion. The questions, about how to behave and respond emotionally, are each followed by a few lines of advice such as: "Always try to gain some insight into yourself, remember that your own needs and wishes are important, and that you should not always give way to others in order to preserve the peace." Eysenck and Grossarth-Maticek have considered whether the powerful effects could be a non-specific benefit of any psychotherapy. However, they have shown that approximately 8% of those with a cancer prone personality who had previously undergone psychoanalysis had died of cancer after nine years, compared with only 1% of a group matched on age, sex, personality type, and smoking but who had not had psychoanalysis. Unfortunately, the investigators do not comment on the discrepancy with their earlier results showing a 39% mortality due to cancer after 10 years in those with the type 1 personality.

There is another noteworthy aspect of these trials. Randomised studies of psychotherapy have rarely achieved such large sample sizes and it is striking that all the individual and group therapy was given by Professor Grossarth-Maticek.[8] The trials were undertaken between 1972 and 1974 and involved 96 subjects (or perhaps 192 subjects, see below) in at least 20 hours of individual work, and at least 10 groups (245 subjects with 20-25 in each) for six to 15 sessions each. Add to this Grossarth-Maticek's explanatory introduction to bibliotherapy for 600 people, and it can be seen that the amount of time spent by this single senior academic on his experimental psychotherapies is huge and certainly unprecedented.

Problems with these investigations

It is unfortunate that Eysenck and Grossarth-Maticek omit the most basic information that might explain why their findings are so different from all others in this field. The methods are either not given or are described so generally that they remain obscure on even the most important points; despite lengthy study of the various papers we are still uncertain just how many surveys were conducted in Heidelberg between 1972 and 1974. Also, essential details are missing from the results, and the analyses used are often inappropriate.

The two recent papers contain many errors. Some are so flagrant that they raise questions about the judgment of the referees and members of the editorial staff of *Behaviour Research and Therapy* who were concerned. For example, in the first randomised trial of psychotherapy Eysenck and Grossarth-Maticek describe in detail how they individually matched 192 pairs of participants. But they report results on only 192 subjects. No attempt is made to explain this remarkable inconsistency; either there have been no less than 10 elaborate misprints or misstatements in the description of the methods, or else there are no outcome data on exactly half the original participants. This last reason could, at least, help account for the "potentially revolutionary results."

As these results are potentially so revolutionary, the following questions must be addressed by the authors.

(1) Why have the descriptions of methods and analyses been left so vague, even after such long delays in publishing this work?

(2) How many surveys were conducted in Heidelberg between 1972 and 1974? Are we correct in thinking there were five separate investigations involving not less than 32 363 subjects?

(3) How was the personality typology applied to participants in the early investigations? In their early results, cancer was associated with "interpersonal repression"[15] and something called "rationality/antiemotionality."[29] Only later was the four category typology applied to the existing data, and details on how this was done have not been published. Without this information one is left to speculate whether the authors have made the mistake, during reanalyses of their data, of reassigning individuals to personality types after causes of death were known. This seems the only possible reason for the very strong disease associations, especially since characterisation of the cancer prone personality has changed over the years.

(4) What is the explanation for the fact that in the description of the methods reference is made to 192 carefully matched pairs of subjects, but the results are reported in only 192 subjects?

(5) Why did the unfortunate control subjects in their randomised trials have such high mortality?

(6) Why did type 1 and type 2 subjects have such low mortality in the investigations aimed at showing the dangers of psychoanalysis?

It is perhaps not surprising that this work has been largely ignored by scientists and clinicians. One comprehensive critical review of psychogenic influences on cancer devoted a single sentence to Eysenck and Grossarth-Maticek's research programme, dismissing it as "simply unbelievable."[16] It could be argued that the numerous errors, the failure to give adequate information about the design and analysis of epidemiological and clinical studies, and the authors' apparently unquestioning acceptance of their own claims indicate that these investigations are not worthy of our current scientific attention. However, they are being used to challenge public health interventions against major diseases,[17-20] for example when they declare that smoking presents the danger of lung cancer "only for individuals of Type I."[5] Also, they complicate matters for other research workers who are attempting to explore psychological influences on the development and outcome of major diseases.

For these reasons there should be a total re-examination and proper analysis of the original data from this research[21] in an attempt to answer the questions listed above. The authors give their address as the Institute of Psychiatry in London, which must be concerned about protecting its reputation. Therefore the institute should, in our view, assist in this clarification of the meaning of the various studies. There should also be some stern questions asked of the editors of the various journals involved, especially those concerned among the editorial staff of *Behaviour Research and Therapy* who, in our opinion, have done a disservice to their scientific disciplines, and indeed to Professors Eysenck and Grossarth-Maticek, in allowing this ill considered presentation of research on such a serious topic.

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(Accepted 18 March 1992)

Current Issues in Cancer

Lung cancer

Robert Souhami

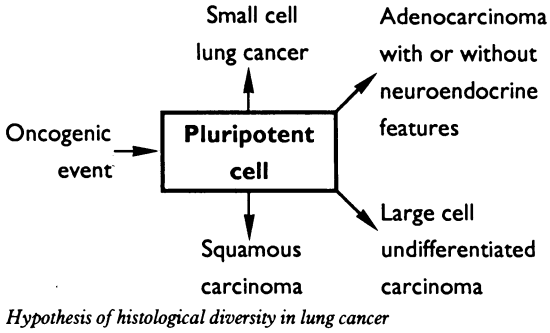
This is the second in a series of articles examining recent developments in cancer

In 1985 there were 29 000 cases of lung cancer in men in the United Kingdom and 11 500 in women. The chance of a man getting lung cancer during his life is 8% and for a woman 3%. It is the commonest cancer in men and the third commonest cancer (excluding skin) in women. Even though young people—especially of social classes A, B, and C—are giving up smoking, the habit is still common, and national governments and the European parliament are reluctant to spend money on prevention or to pass effective legislation to reduce cigarette advertising. Nevertheless, there is evidence that the death rate from lung cancer is falling in men aged 20-44,[1] although that in women is not. In the professional lifetime of most of the readers of this article, lung cancer will remain an important cause of death from cancer.

Although the dominant cause of lung cancer is smoking, the disease is curiously diverse histologically and in its clinical behaviour, and management is correspondingly varied. For this reason it is wrong to generalise about treatment and prognosis in lung cancer and, in most cases, there is every reason to seek expert advice.

Biological aspects

The main disease forms and their frequencies are squamous (epidermoid) 50%, adenocarcinoma 15%, large cell (undifferentiated) 10%, and small cell 25%. These frequencies may be changing in the United States and Japan, where adenocarcinoma seems to be predominating in the non-small cell lung cancer category. What is the origin of this curious diversity of histological form? The figure shows a reasonable hypothesis. The cancer inducing event may occur in a pluripotent cell capable of differentiation along different pathways. This might explain why "mixed" tumours (adeno-squamous, small cell-squamous) sometimes occur. Progression of cancer is accompanied by, as in other cancers, genetic change, including mutation in the p53 gene (the product of which is a nuclear phosphoprotein involved in cell division)[2] and a characteristic loss of part of the short arm of chromosome 3 in small cell lung cancer, whose functional significance is unknown.[3] Other genetic changes, which occur more variably, are overexpression of the myc family of oncogenes and abnormalities of the retinoblastoma gene structure or expression. It is not known how these important abnormalities are involved in the origin, or the continuation, of tumour growth.



Hypothesis of histological diversity in lung cancer

The different histological types of lung cancer have their counterpart in cell cultures derived from human tumours. Study of these cell culture systems has identified factors which regulate cell growth and has helped to define the particular characteristics of the different tumour types. In cell culture the small cell cancer exhibits a neuroendocrine phenotype. The cells express neural antigens, synthesise and secrete peptides such as antidiuretic and adrenocorticotrophic hormones,[4] and show the sensitivity to cytotoxic drugs that characterises small cell cancer. Several of the peptide hormones (such as gastrin releasing peptide) are secreted by the cell and also bind to the cell surface after secretion. Binding to the surface receptor activates division of the cell that secreted the peptide—so called autocrine growth stimulation.[5] These important growth regulatory mechanisms open up possibilities that we may one day be able to block autocrine stimulation of cell growth as part of a treatment strategy. Adenocarcinoma of the lung may also show some neuroendocrine characteristics in both cell culture and tissue

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Series edited by: Dr G M Mead.

BMJ 1992;**304**:1298-301