Alive to Forty-Five

Proceedings of a Symposium

held at the

College of General Practitioners, London

Sunday, 27 November, 1966

OHE

Edited by: George Teeling-Smith

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45

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by the Office of Health Economics

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Foreword

George Teeling-Smith

WHEN discussing the four commonest causes of death among young adults, the principal contributors to this symposium each tackled their subject in very different ways. In publishing them together I make no apology for this. Indeed, it highlights the way in which the challenge of the continuing high level of mortality among young adults in Britain can be approached from different angles. Fundamental research, such as that described by Dr Long, is complementary to the application of medical procedures such as those described by Dr Hamer, and to the more social and educational approach of Professor Gissane and Dr Sainsbury.

Further, their different approaches help to illustrate the fact that the problem must be the responsibility of *all* those who can help. Medical and epidemiological research alone are not enough; nor are good general practice, effective preventive medicine and efficient hospitals; nor are health education or further safety measures. Each one is vital, and all must work together to reduce the present toll of some 24,000 young lives per year.

The Office of Health Economics can do no more than help to propagate progressive thinking about medical care, such as that of the contributors to this symposium. Any consequent benefits for the community -- in this case young adults at risk of premature mortality -- must flow from the actions of those who are more directly concerned with research, with medicine and with patients. It is they alone who can alter the patterns of mortality.
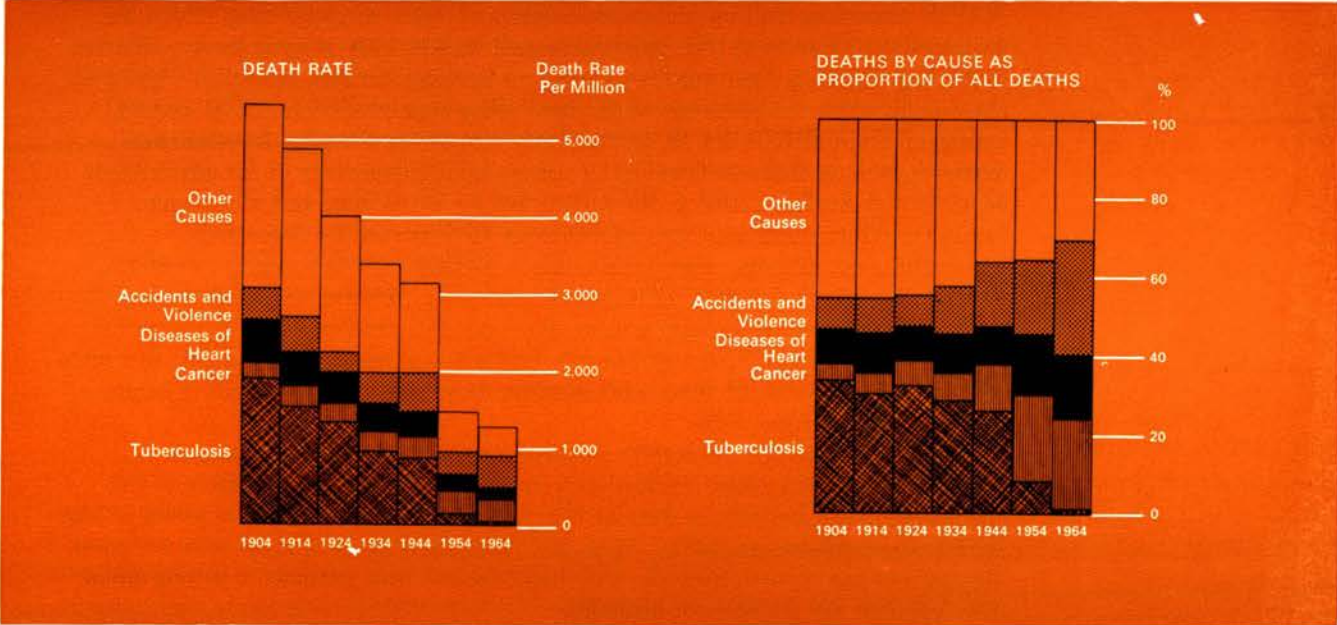
Leading causes of death, all persons, 15–44, 1904 to 1964, England and Wales.
(a) Death rates per million living, and (b) Deaths by specified cause as proportion of all deaths.

Source: Registrar General's Statistical Review, various years.

Introduction

Dr Charles Fletcher

THE ultimate arbiter of the effect of medical practice is to be found in mortality rates. Great emphasis has been laid in recent years on the degenerative diseases of late middle age, particularly in men. The steady decline in mortality which has taken place during this century in both sexes between the ages of 45 and 70 has been halted in men during the past 20 years; for them the mortality rates are now rising although female rates continue to decline. This rising male mortality is largely due to coronary heart disease, bronchitis and lung cancer.

We are perhaps less aware of the challenge presented to us by deaths in the younger age group with which this symposium is concerned. We all know of the tremendous power given to us by antibacterial drugs and of the resulting control of the main cause of mortality at this age among previous generations – the infectious diseases. These we regard as largely conquered. Few of us find time to read the reports of the Registrar General which, though a veritable mine of valuable information, are not light reading. We, therefore, owe a great debt of gratitude to the Office of Health Economics for the excellent statistical reports that they produce, the latest of which provides the background to this symposium.

Looking around those present, I can see that some at least are still in the age group 15–44; others have left that age group and are now in the more dangerous decades beyond; but I, and I suspect several other people here today, belong to those who but for medical advance would have died at an earlier age. Without insulin I would have died some 25 years ago.

The subjects of our symposium are highlighted by the figure reproduced from the report *Disorders which Shorten Life*. The total death rate in the young people between the ages of 15 and 44 today is less than the death rate in the same age group from tuberculosis alone in 1924. Over 70 per cent of these deaths are now caused by accidents and violence, by cancer and by disease of the heart. The total mortality figures are still impressive. The figure of 24,000 deaths in a year is so large as to defy comprehension but this means something like 480 deaths a week or 66 per day. Sixteen people between the ages of 15 and 44 will have died during the six hours taken up by this symposium. Although the symposium does not include the subject of pneumonia I find it most valuable to be reminded of the fact that deaths from this disease continue to occur at a steady rate among young people. There is certainly a need to investigate this surprisingly high residual death rate; one of the 16 deaths during our discussions will be from pneumonia. On the subject of heart disease, which will be dealt with by Dr Hamer, I find it particularly challenging to look at the rising death rate in males since 1947. This is largely due to coronary heart disease which is widely attributed to cigarette smoking. However, this simple explanation will not fit the rapid, rather recent rise unless perhaps it reflects the very great increase in smoking that occurred among men of this age during the last war. Turning to malignant disease, we see the flat and continuing mortality, mostly from leukaemia and brain tumours in the younger patients and from cancer of the lung and stomach in middle aged men, with cancer of the reproductive organs the chief cause in middle aged women. This will be being discussed by Dr Long whom I gather has some exciting hopes for progress to offer. We are also to discuss the depressing figures for suicide – higher in men than in women but both sexes showing a steep rise in recent years. However, this rise may partly be due to the fact that the act of suicide is no longer a criminal offence and may, therefore, appear more readily on death certificates. But we

should also recall that in recent years there has been a similar rapid increase in the income and in education of young people on the one hand and in delinquency, drug addiction, illegitimate births and industrial unrest on the other. Finally, we are to discuss deaths from accidents. In this case the problem is underlined by the appalling steep rise in deaths between the age of 15 and 19 which are largely due to motor bicycle accidents. We must not forget that this increase would have been far greater but for advances in blood transfusion, anaesthetics and for the surgical skill of people like Professor Gissane.

All of these subjects are of interest to those in general practice and in the public health services. It is encouraging that so many are prepared to give up their Sunday to discuss them at this symposium.

How Many Lives Could We Save?

George Teeling-Smith

OUR OHE booklet on *Disorders which Shorten Life* records the very remarkable progress which has been achieved in reducing mortality among the 15–44 year olds, mainly through the control of infectious diseases. For these young adults the death rate was halved in the ten years between 1944 and 1954. Nevertheless, despite this achievement a very real challenge remains. The urgency of this challenge is underlined by the fact that the sharp decline in mortality among young adults slowed down after 1954, and has halted altogether in the last five years. Since 1960 there has been a fairly constant annual death rate, taking a toll of about 24,000 young lives each year. Almost three-quarters of these deaths are caused by accidents, cancer, heart disease and suicide, which are the subjects of this symposium.

Before the experts discuss these four subjects, I would like, first, to turn the problem into human terms; I would also like to speculate on how many of these lives we might be able to save; finally, and most important, I want to discuss some of the economic factors which may influence our success in meeting this challenge.

First, then, let me put the young adult mortality figures in terms of the individual lives they involve. At the present rates, one girl in every thirty-five and one boy in every twenty-two who leaves school this year will die before reaching their forty-fifth birthday. A further one in thirty will lose a brother or sister in the same period. In addition, one boy in forty-five will marry and lose his wife before the age of 45; similarly one girl in thirty-three will marry and lose her husband. Thus, unless we improve on the present pattern of mortality among young adults, from an average class of thirty school leavers this year, we can expect three to die or to be bereaved of a spouse or sibling before they reach middle age.

Second, how many of these lives could we save? You will be hearing later today some forecasts of probable progress from our four experts. Because it is difficult for them to be specific, I would like to give some overall estimate of the number of deaths we should soon be able to prevent. To justify my stepping in where angels, very properly, fear to tread, I would like to quote a sentence from Galbraith's first Reith lecture this year: 'It is a commonplace of modern technology that there is a high measure of certainty that problems have solutions before there is

knowledge of how they are to be solved'.

There are several areas where I believe we should be able to find at least partial solutions in the near future. These include the prevention or cure of the remaining infections; the earlier detection and more effective treatment of some of the cancers; the prevention of the few deficiency diseases; the provision of intensive care units to cut down mortality from coronary heart diseases; the reduction of accidents on the road, accidents by poisoning and by drowning; and some reduction in suicide. Quite conservatively, I estimate that we could save between 6000 and 7000 lives a year, out of the present total of 24,000 young deaths, if we are to concentrate research, available medical facilities, and, in the broadest sense, health education on these subjects.

Incidentally, it is also interesting to look at the comparative mortality rates for the different diseases in this age group in different Western countries. If we were, quite arbitrarily, to assume that the rates in Britain for the four main causes of death could in each case be reduced to that of the lowest country, it would again mean a reduction of somewhere over 7000 deaths a year.

Thus, although any such estimate must be speculative and arbitrary, I do not think it unrealistic to say that if our resources are concentrated on this problem we could very quickly reduce the present young adult mortality rates by at least a quarter. This brings me to my third question. How are we to ensure that our resources are concentrated in this way? What other priorities are claiming equal or greater attention?

The most important point to remember is that, essentially, it *is* a question of priorities. We are now all beginning to realise the myth of Beveridge's promise of a health service which could 'ensure that for every citizen there is available whatever medical treatment he requires in whatever form he requires it, domiciliary or institutional, general, specialist or consultant'. Medical progress, particularly in such fields as brain and heart surgery, and with organ transplantation, has recently highlighted the fact that the latest and best medical care must always be a scarce commodity. Its availability must be restricted, under any system of medical care, to what we are, individually or collectively, willing and able to provide. Housing, roads, education and defence compete in the public sector for resources which could otherwise be devoted

to health. Public expenditure – which must inevitably finance the lion's share of the cost of medical care and research – competes with private expenditure. As taxpayers and electors we jealously guard the share of our income which we can keep to spend personally; and in this country, at least, very little of our private expenditure is voluntarily allocated to supplement public expenditure on health.

I have argued elsewhere that the total share of our national resources devoted to health is too small. Today, I want to mention more specifically the problem of allocation within the total health budget. If, as I have suggested, money – and all that it means in the form of research, facilities and education – could at present save 6000 young lives a year, should we not allocate the funds for this obvious priority? The problem, of course, is that we can only do so at the expense, for example, of slowing down the rate at which we improve the infant welfare services or the provision of care for the elderly. In addition, it is sometimes impossible to direct medical care specifically to a narrow age group, and sometimes the avoidance of a young adult death will leave long-term disability. I do not think there are easy answers to questions of allocation of resources; but I think it is quite wrong that we should ignore them just because they are difficult or unpalatable.

I would like to introduce one other thought at the start of our symposium. If, as I believe, we could save 6000 young adult lives a year by concentrating our attention on some of the more easily soluble health problems of this age group, the survivors net contribution to the economy would be equivalent to some £30 million. That is, the current net value of the economic contribution of each person saved is equal to some £5000. I wonder if it would really cost as much as that to save these lives? If not, it is ridiculous not to find the resources which could achieve this reduction.

The cost of sickness, and the benefits of health, must always be measured primarily in human terms; but I do not think we can ever leave the pure economics out of the equation.

Suicide

Dr Peter Sainsbury

IN order to direct my remarks on suicide towards the problem of its prevention, I will first say something about statistical and epidemiological studies on suicide, because they provide a method for identifying those groups in society most at risk, as well as social and other factors predisposing to suicide. Secondly, I will refer to some case-studies of suicide and the suicidal patient to see what we can learn from this source about recognising the younger suicide and his clinical characteristics.

Epidemiological Aspects

Among the many significant facts in *Disorders which Shorten Life*,[1] is a very unexpected one: that suicide is a major cause of death in young people. It shows, for example, that one in ten deaths in the age group 25–34 is due to suicide. This high figure probably surprises us. That it does so draws attention to one of the obstacles in preventing it: what is it about our attitude to suicide which allows us to disclaim the same sense of responsibility for its prevention which we readily accept for the other conditions to be considered today? Do our pre-Freudian and pre-Durkheim notions about suicide still cause us to regard it as a moral rather than a medical or social problem?

Suicide, it is often claimed, is a condition which is in some way bound up with social processes, and particularly with factors in the social environment generated by modern society such as urbanisation and the impoverishment of family and religious life. When the suicide trends are examined in this and other countries, which have kept records for the last fifty years, the pattern that emerges is fairly clear. The incidence of suicide in young people has decreased in most countries; the decrease has been more marked in men than in women, but women over forty have shown a striking increase in their suicide rates.[2] The spectacular changes in westernised society have not therefore by any means been uniformly harmful; though women in their forties have for some reason become more vulnerable. Nevertheless, women continue to have a suicide rate which is about half that of men: an interesting phenomenon, which occurs with the utmost consistency everywhere and at all times, but the disparity between the sexes is becoming decidedly less in the young. I will deal with suicide by sex and by age in more detail to search for further clues.

In both sexes suicide rates are always found to increase sharply with age: between the second and third decades the rate doubles, and in males a peak is reached at about sixty-five – it occurs some ten years earlier in women. These increases and peaks would appear to relate to those periods in life when an individual's situation in society changes critically. Children leave their families around twenty for example, and men retire from their occupations at sixty-five.

An instructive exception to the finding that the suicide rate in young people is decreasing in most countries was recently reported from Tokyo. In 1955 the suicide rate for men aged 20–24 soared to 80 per 100,000, and to 47 per 100,000 for young women.[3] That is about 20 times the rate found in this and most other countries. Such a remarkable epidemic of suicides invites an explanation, and one in terms of social events seems unavoidable. One hypothesis might be that the traditional values and norms of Japanese culture had become so disrupted by the social consequences of the war and the American occupation that the young lost sight of the standards and goals which ordinarily give life meaning and purpose. These hypothetical ideas would be more meaningful if they were successfully to predict the incidence of suicide in a given social group.

To give an illustration of what I mean I will compare suicide in the aged with that found in the young. I predicted that if the elderly are predisposed to suicide because they have no recognised function in society and no useful occupational status, then the age–specific rates in a society which valued its elderly members would not show the usual pattern of low rates in the young and high ones in the elderly. Yap, a psychiatrist in Hong Kong, produced the figures I had looked for in vain. They were those for suicide in Pekin in 1922, a time when ancestor reverence was still a customary part of Chinese culture. They clearly showed that the invariable pattern of suicide was reversed: the younger age groups had the high rates and the aged the low ones.[4] More recently Asuni reported on suicide in Nigeria and the rule was again broken: the rates of tribal Africans did not show the usual increase with age.[5] These observations seem to lend some support for the view that the relation between age and suicide really is an effect of identifiable social processes.

I have suggested that lack of occupation in our society is perhaps one obvious way in which a man may become socially isolated; and suicide rates among unoccupied males are in fact much higher than among the employed.[6,7] The figures published by WHO on suicide in twenty countries are also relevant here.[8] If the mean suicide rates for the period 1921–22 are compared with those for 1931–33, the time of the world economic depression, the incidence of suicide can be shown to have increased everywhere – particularly in men and women in their forties.[2] Poverty appears not to have been the explanation, because in England the unskilled workers in Class 5 had the lowest class rates during the depression; suicide was highest and had increased most among the professional and managerial classes. These findings imply that both lack of work and loss of social and economic status are more important in suicide at this age than is destitution.[6] Moreover, in general, suicide has a higher incidence in the upper socio-economic classes;[6] though this does not hold consistently for all the younger age groups. The top educational groups, however, are also found to be more suicide prone. University students, particularly those from Oxford and Cambridge, have a rate significantly above the corresponding age groups in the general population. One in three of Cambridge undergraduate deaths are from suicide.[9] Do positions of wealth and prestige carry more risks of losing status? Are top people, in short, more exposed to the hazards of social mobility? Those who have belonged to and accepted the values of one social class may fail to readjust, and become isolated and adrift when they move into a different one.

Another common finding, of an opposite kind, is that suicide decreases in war time; so regularly does this happen that it may be said, even if England's psychiatrists do not know how to prevent some 1500 suicides a year, at least her sociologists do: they would recommend a declaration of war. Everyone of the countries actively engaged in World War II showed this decrease.[2] In war time there is full employment but social integration also increases in times of national crisis.

The notion that suicide increases when social integration and social regulation are weak was first put forward by Durkheim in 1897.[10] Social integration, according to Durkheim, is manifest as the 'common conscience' of a community: those beliefs, customs and values that members of a society share; and suicide occurs when integration is diminished. Social regulation, on the other hand, is the control which a society exercises over its members. If this is weak goals and ambitions are unlimited and the purposes of life become ill-defined. In these circumstances members of a society are also predisposed to suicide. I think the concept of social integration and its converse 'isolation' subsumes both processes. Be that as it may, one way in which Durkheim tested his theory was by relating suicide and integration within the family group; and his observations on marital status are as valid now as they were in his time. Allowing for age, the divorced and separated have the highest rates of suicide, the single and widowed come next and the married have the lowest rate, which is just what his theory required.[11] Moreover, the suicide rates of the married decrease progressively as each child is added to the family: there is, however, a limit to this felicitous state of affairs: it no longer holds after the fifth child.[12]

I don't want to overstress the sociologist's view-point so I will conclude this part of my talk with one last illustration. Urban rates of suicide are higher than rural ones, among the young especially; and exceptions to this rule are few. I attempted to see whether, by a more detailed analysis within the city, social isolation could be shown to be associated with urban suicide. Various indices of isolation, such as the rates of living alone in digs or boarding houses and of foreign-born persons, were calculated for the twenty-eight London boroughs and correlated with their suicide rates. A very significant association was obtained; but as these statistical relationships might be artefacts, the coroners' records of the suicides were also examined, and I was able to show that the suicides were in fact living alone; were more often foreign-born; and incidentally, poorer, than were the population at risk.[6]

This seems an appropriate point at which to summarise this actuarial and sociological approach to the causes and prevention of suicide. Social factors are clearly important in determining the incidence of suicide in a community. Precisely how this social component should be defined is uncertain; but the concept of social isolation seems to be a useful one, because isolated social groups and socially isolating events are consistently associated with a high incidence of suicide. Such observations on social factors

predisposing to suicide indicate what social action is needed to prevent or diminish its incidence. The other practical consequences of this statistical reconnaissance has at least been to show that certain groups in the community below the age of forty-five are more at risk than others. Thus, with each decade of life the risk nearly doubles; the male student living alone in a city is especially vulnerable; and the well to do single woman approaching forty-five is becoming increasingly so.

Clinical Aspects

Suicide arises from the combined effect of a number of factors. I have just attempted to show that epidemiologists by studying groups or populations recognise various social factors as important. Psychiatrists investigating the individual case point to other factors, but at this stage of our knowledge it is difficult to reconcile the social and clinical findings. Case studies based on the perusal of coroners' reports, the clinical examination of psychiatric patients with pronounced suicidal feelings and of attempted suicides, emphasise the interaction of a morbid personality and psychosocial stresses.

The first question which might be put to the clinical psychiatrist is to what extent is the balance of the suicide's mind in fact disturbed? In other words what proportion of suicides have a recognisable mental illness? What illnesses do they have? and are they treatable ones?

When psychiatrists examine the coroners' records they find, irrespective of age, that about one-third of suicides have a mental illness which they can recognise; and this is in spite of the records being most unsuitable material from which to make a diagnosis. The proportion rises to about two-thirds if the suicides' previous medical records are also traced. Recently Robins and his co-workers in St Louis visited the homes of all suicides soon after the event and obtained detailed clinical information about them from relatives. They concluded that no less than 94 per cent of the cases were psychiatrically ill and a further 4 per cent were suffering from a terminal medical illness: the other 2 per cent appeared to be well.[12] I think these findings are of the utmost importance. Furthermore, Robins also found that 68 per cent of the suicides were suffering from one of two diseases: either manic-depressive illness or chronic alcoholism; but if

the cases in which they were unable to agree about the psychiatric diagnosis are excluded, then 83 per cent of the remaining 109 suicides belonged to one or other of these two categories.

As depression was diagnosed in over half the cases I would like to consider this condition further.

Their high risk of suicide is confirmed by studies in which depressives have been followed-up for a number of years: they agree in finding that between 14 and 17 per cent will eventually die from suicide.[12, 13]

Unfortunately there is very little information on the interaction of age and mental illness; but Robins has observed that the age of the manic-depressive is an important factor in evaluating the probability of suicide. This illness starts before forty in half the cases, but only 8 per cent of his depressed suicides were below this age.

When manic-depressives with suicidal ideas were compared with non-suicidal depressives, Walton found that the suicidal ones had been bereaved in childhood to a significantly greater extent.[14] Both age and bereavement therefore increase the risk of suicide in this condition.

Certain clinical facts about depression are also important from the point of view of its recognition and prevention. First, it is a very common illness, and the clinical picture is as characteristic as that of measles: it should be more readily recognised than it is. Secondly, the less spectacular form of the illness, not stressed in the text books, also carries a risk of suicide. I mean the person who says he feels tired and finds everything an effort. Typically, he is neglecting his usual social activities and interests, and he harps on some minor bodily symptoms. He is sleeping badly, waking early and losing weight. He is becoming indecisive, self-critical and views the future with foreboding. Such men are dangerous.

Ominous symptoms which point to suicide in the flagrantly depressed person are, agitation, marked hopelessness, and delusions of worthlessness, of sin and of incurable disease.

Thirdly, depression may masquerade as irritability, a paranoid state, or as preoccupation with a physical symptom and in these cases the depressed mood is often denied, but the other symptoms are there. Next, the manic-depressive is very amenable to treatment; 80 per cent remit with ECT or drugs. And lastly, the depressed patient will usually discuss

his suicidal ideas openly with his doctor and in such a way that an evaluation of the risk of suicide can be made and admission to hospital arranged when there is any doubt about his intentions.

The second condition featured so prominently in Robin's study was chronic alcoholism. I don't believe we will find the same high incidence of alcoholics in our suicides, but that does not alter the fact that the risk of suicide in these patients is considerable. Kessel in a follow-up study of alcoholics treated at the Maudsley found 8 per cent had committed suicide over an average of five years,[15] while Helgason in an epic survey followed a sample of the population of Iceland through sixty years and found those who had become alcohol addicts had a 5·5 per cent expectation of suicide.[13] The systematic management and support of the alcoholic after discharge from hospital is therefore essential.

Other common mental illnesses in this age group may also terminate in suicide. About 2 per cent of *schizophrenics*, according to Helgason, will eventually commit suicide; but *psychoneurotics* seldom kill themselves, though they are conspicuous among those who attempt suicide.

Whether various abnormal personalities such as the inadequate, dependent, drifter type of psychopath; or the hostile, aggressive impulsive ones are particularly suicidally prone is difficult to determine retrospectively from coroners' records. Similarly, we would like to know whether other types of personality, who fall within the range of what passes for normal, are predisposed to suicide: rigid people, for example, who cannot readjust to changes in their circumstances;[16] or the solitary, taciturn, over-serious and depressively inclined. This is a psychological aspect of the problem which urgently needs studying, especially in the young suicide.

The last category of people with a high risk for suicide I will speak about are attempted suicides: a group which is largely confined to the under forty-fives. But I want to stress that those who attempt and those who commit suicide are two different populations: their demographic, social and clinical characteristics are very dissimilar.[2,17] Thus more women attempt suicide; more young people do so; it is commoner among the married, and neurotics and personality disorders seem to predominate. The opposite, in fact, to what is found with suicides. But

clearly the two populations overlap to a considerable extent, as some serious and determined attempts to die fail and vice versa; consequently every suicide attempt must be carefully assessed to determine whether a second and consummated one will be made. Kessel, with some justification, prefers to avoid the word suicide when referring to these cases; he speaks of acts of self-poisoning and self-injury. He reported that 19 per cent of 511 cases of self-injury admitted to a special ward for their care at the Royal Infirmary, Edinburgh, had repeated the act within a year, and 1·6 per cent had killed themselves.[18] This figure does not differ substantially from that obtained in other follow-up studies of attempted suicide.

The attempted suicides who are most likely to repeat the act and to kill themselves are those with a depressive illness, with alcoholism or with a psycopathic personality; or combinations of these.

The *methods* used by suicides and attempted suicides also point to their behavioural differences and to probable differences in their psychopathology. Suicides usually plan their death carefully. It has the appearance of a premeditated act, deliberately undertaken to avoid discovery and to ensure death. Though barbiturates are often used, large doses are taken. More commonly, however, the methods they use are the ones most likely to be lethal; carbon monoxide poisoning, shooting, hanging and drowning. With attempted suicides, on the other hand, the suicidal act is unplanned, impulsive and undertaken in a way which invites discovery. The methods are less certain. Barbiturates and aspirin, in varying doses, are by far the commonest; then wrist cutting. Their intention more often seems to be an attempt to cope with a problem which has become unmanageable, rather than to die: Stengel has drawn our attention to the attempted suicides' 'cry for help'.[17]

This brings me to the other factor in suicide: the situational one. The stresses and crises which appear to precipitate it. They are the same misfortunes everyone encounters; but since only 1 in 10,000 resorts to suicide, the problem is one of describing and recognising the sort of personality who is unable to adjust to changes and stresses.

Whereas in the elderly bereavements, loneliness and physical illness, are the stresses which most frequently precipitate suicide; in the young it is troubled personal relationships which do so.[7] Unemployment is also

important. Marital, amorous and family discord stands out in this age group; and they account for the majority of cases of attempted suicide as well.

Drunkenness at the time of suicide is not common in the young;[19] the contrary to what is found with attempted suicides, and physical illness contributes to about only 10 per cent of suicides at this age. A physiological factor in suicide was interestingly demonstrated in another way by McKinnon and McKinnon.[20] They examined the endometrial sections of twenty-three young women who had committed suicide and only one was found to be in the follicular phase of the menstrual cycle.

The bulk of young suicides are therefore recruited from a few well-defined categories of mentally ill people; and they will be suffering from either depression or chronic alcoholism, or will have previously attempted suicide. There is also probably a group of people with personality disorders which may be quite important in the under forty-fives.

I hope what I have so far said about psychiatric illness in suicide, its incidence, its clinical recognition and the risk in different diagnoses, will have indicated that prevention is both feasible and mandatory.

We found that 20 per cent of suicides in Chichester had had contact with a psychiatrist in the preceding year,[21] and Capstick found that about 7 per cent of suicides had been in-patients, the most dangerous time being immediately after discharge.[19] The same author also reported that about 78 per cent of suicides had been under medical care in the 'months' preceding death, and that 60 per cent had communicated their intentions. Robins' figures were similar, but he adds that the suicidal communications were repeated to many people in most instances, and that 53 per cent of the important manic-depressive group had received medical or psychiatric care in the four weeks preceding suicide. It therefore seems that neither the psychiatrists, nor G Ps nor laymen are able to evaluate these warnings effectively, and this is disturbing when one considers how treatable many of them are. I have only left time to enumerate some steps which might be taken to improve the situation.

I believe first, that more stress should be placed in medical education on the recognition and treatment of depression and other common or garden psychiatric conditions; and particularly on the systematic examination and evaluation of the suicidal patient.

Secondly, since depression so commonly precedes suicide and because it is closely associated with seriousness of intent, the symptoms indicating a risk of suicide should be known and always looked for in depressives. The treatment of depression is effective, but it is important that the subsequent follow-up should also be thorough: half-treated depressions and those recovering or recently discharged from hospital are known to be a risk.

Similarly, alcoholics being treated in the community also need regular supervision and support from someone. This need not necessarily be his doctor; but it does need to be somebody such as a social worker, a Samaritan or an anonymous alcoholic with whom rapport has been established, who can be relied upon and who can be turned to when things get bad. Thirdly, we should learn to pursue any threats or hints of suicide that patients and others offer, by openly discussing with them their attitude to suicide and to death, and if there seems to be any doubt ensure that an expert opinion is obtained. Fourthly, those who see attempted suicides should have a set procedure for the psychiatric and social assessment of all such patients to ensure that the seriousness of the attempt is evaluated, the patient's diagnosis and problems formulated, and a definite programme for her subsequent management and after care decided upon.[22] Fifthly in every district there should be either a casualty department or emergency ward equipped to deal with both the medical and psychiatric aspects of self-poisoning and other self-injuries, which is known to all non-medical as well as medical people as a place where the suicidal can get help.

I will end with an optimistic note: some experimental evidence that with improved psychiatric services it may be possible to reduce the incidence of suicide in patients. In this instance psycho-geriatric ones, but it illustrates the practicability of prevention. In 1958 a community psychiatric service was introduced in Chichester in which most patients are treated either at home, as out-patients, or in a day hospital rather than by admission. The new service enabled more elderly patients to obtain psychiatric treatment. Dr Walk wanted to find out what effects a service of this kind has had on suicide. He therefore calculated the proportion of suicides occurring in our district that had been known to a psychiatrist some time in the year preceding death; he did this for the five-year

period before the introduction of the service and again for the five years after. Four out of nine suicides over sixty-five were known to the psychiatrist before the service was started, but none of the twelve suicides in the area were known to him following its introduction. The suicide rate in the patients had decreased significantly, therefore, and this had occurred in spite of the number and rate of referrals having increased in the second period.[23] Did the service prevent them?

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Road Accidents

Professor William Gissane

THE Registrar General's Statistical Reviews of England and Wales show that whilst death rates from accidents generally have not increased during the last sixty years, those from traffic accidents have risen from 21 per cent in 1904 – the train and horse era – to 66 per cent in 1964 – the motor vehicle era.

It is perhaps remarkable, in this age of mechanisation in industry and the home, that the overall accident death rates have not increased; that they have not must be attributed to many factors, but once the accident has resulted in severe injury, the main credit must be given to advances in treatment.

Advances in Medical Treatment

The most recent of these has been the use of helicopters for the gentle, very early and speedy transport of the seriously wounded to forward placed, fully equipped and staffed hospitals in the Korean campaign. This resulted in the lowest mortality and morbidity rates in the history of warfare. Before that, early and adequate blood transfusion was shown as essential as the prevention of wound shock. Later, if adequate respiratory function after serious chest injuries was not restored before transfusion, more blood could embarrass the pulmonary system. So surgical methods were developed to quickly restore adequate respiratory function.

Anaesthetic risks after early and adequate respiratory and circulatory resuscitation then became almost non-existent, with great advances in anaesthesia. Next it became possible to apply surgical techniques developed in the various specialties to the most severe types of injury and safely explore all body areas.

Antibiotics and clean air operating theatres and dressing stations have now tamed the infections.

If all these advances were made readily available to all injured people through modern hospital accident departments on a national scale, greater reduction in accident death rates, in permanent disablement and in prolonged hospital care would follow. But these would be less marked with traffic accidents than in others, such is the present severity of road injuries. We must therefore seek ways of preventing these injuries or of lessening their present severity. This is the subject matter of this paper.

The Problem

That the death rates from traffic accidents have more than trebled during this century is due to what may be called 'A transport revolution'. Motor vehicles now carry about 80 per cent of the total national passenger and freight loads. This requires some 13 million vehicles and even more drivers. We are not only short of road space for vehicles, we have also run out of drivers capable of safely meeting this heavy transport responsibility.

Last year over 100,000 people were seriously injured, including 8000 deaths on the roads of England and Wales. In no other ordinary activity are so many people killed and seriously injured. Road accidents will undoubtedly continue until in the foreseeable future developments in electronics take over a large part of the control of motor vehicles and their maintenance. I am told that this will take some twenty years. In the meantime we are concerned with the present situation.

As surgery turned to the engineer for much of its modern hospital equipment, it turns again to road and vehicle engineers and designers to give greater protection to all road users, and even more important, to the road users themselves and their medical advisors. Let us start by examining the road users now involved.

With us, pedestrians are still the most frequent victims, accounting for 40 per cent of all our road deaths, the young and the old constituting the major part of this problem. Another 25 per cent involve the riders of two wheeled vehicles, mostly motor cyclists and youngsters. The remaining 35 per cent are occupants of other vehicles – mostly cars and largely younger males. It is this last group that are of growing importance, for the increasing car occupant involvement can be directly related to increasing numbers of cars. During the decade ending in 1963, the numbers of cars doubled and car occupant deaths rose from 17 to 34 per cent of all our road fatalities. Now one occupant is killed for every 4000 cars per year.

Other countries have different rates and proportions. In the United States the road death rate per head of population is twice as high as ours, but they have many more cars. With them over 70 per cent of their road deaths involve car occupants, one being killed for every 2000 cars per year. Yet their motor vehicle fatality rates per 100 million vehicle miles are, at 5·4, the lowest of any country. Several European countries also have high and increasing rates for car occupants.

Pedestrian death rates do not show a similar relationship to the increasing numbers of cars, instead they are a relatively constant proportion of the pedestrians at risk – about one death per 20,000 inhabitants per year.

All these accidents concern human behaviour. This can be usefully viewed as a failure of competence to perform the tasks set by various road situations which all too frequently outstrip the road users' abilities, particularly the younger road users' abilities. My colleague, Dr John Bull, a research scientist, has examined the evidence of the human factors related to car drivers and their accidents, and has made some interesting and important assessments which he maintains are guesswork, but guesswork based on published research including Borkenstein's important work on the effects of alcohol. From this study, Bull estimates that there would be perhaps a 10 per cent improvement in road accidents by better training and by the retraining of incompetent drivers, another 10 per cent by the strict enforcement of existing traffic regulations, another 10 per cent by excluding alcohol, and perhaps another 1 to 2 per cent by more stringent medical standards of fitness to drive. These are reasonable assessments on the available evidence of the improvement to be expected from an all-out effort to manipulate human behaviour in order to prevent the first phase of the accident sequence, that is the circumstances that lead up to the crash or its avoidance. These events do not exclusively concern a driver's behaviour; other road users are also involved as is the vehicle, the road, the weather and other factors.

Efforts to manipulate human behaviour are not easy and will take time, but they must be pursued.

Let us now turn to the second or crash phase of the sequence. In it the forces of impact – depending on their characteristics – and the degree to which they have been anticipated by the road users themselves – by vehicle and highway crash design – do their work harmlessly or with considerable human damage. The mechanisms of these injuries are common to all road users and it seems that they are still prepared to expose themselves to crude and overwhelming forces of energy, and the young more willing to 'risk their necks'.

The pedestrian, after the initial impact, generally by a car, becomes a projectile, to be thrown upwards if hit low, or directly downwards if hit at or above centre. Then secondary impacts follow of much greater violence against the road, roadside furniture, other parts of the vehicle, or passing vehicles. These secondary impacts are responsible for the multiplicity of grave pedestrian injuries.

The riders of two-wheeled vehicles – and motor cyclists are mainly concerned – enter their traumatic experience at speed and in a sitting and very exposed position. After receiving direct impact injuries, they too are projected often very considerable distances to receive secondary injuries on average more severe and multiple than those of other road users. The risks of injury to motor cyclists are twenty times greater than car users for comparable distances travelled – about one motor cyclist is killed per 1000 motor cycles per year.

A major mechanism of injury to car occupants is again of the same projectile type. After their vehicle's collision they move off their seats at about the vehicle's pre-crash speed. But unless doors open their flight path is usually restricted to the dimensions of the passenger compartment of their vehicle.

Front seat occupants are between three and four times more vulnerable than those in rear seats. (Figure 1). Their knees first impact the glove cupboard, then their heads the junction of the roof and the windscreen, next their trunks impact the steering assembly or the dash. Thus from this projectile pattern and the resulting impacts, injuries occur to the knees through to the femur and the hip joint, fractures to the skull, injuries to the brain and the neck, multiple fractures of the ribs, injuries to the lungs and main air passages, ruptures of the aorta, generally in its arch, injuries to the heart and multiple injuries to abdominal organs. This pattern has been confirmed by our studies of over 400 autopsy records.

In car crashes there is another major mechanism of injuries – the deformation or penetration of the passenger compartment onto its occupants.

Reviewing our studies of the causes of car occupant deaths, we attribute the projectile and the deformation mechanisms as responsible for equal numbers of deaths. Deaths from extensive body burns were responsible in this study for 2 per cent of car occupant deaths when the collision resulted in the escape of petrol due to damage of the tank or its feeder pipe, the subsequent ignition of this petrol, and the inability of car occupants
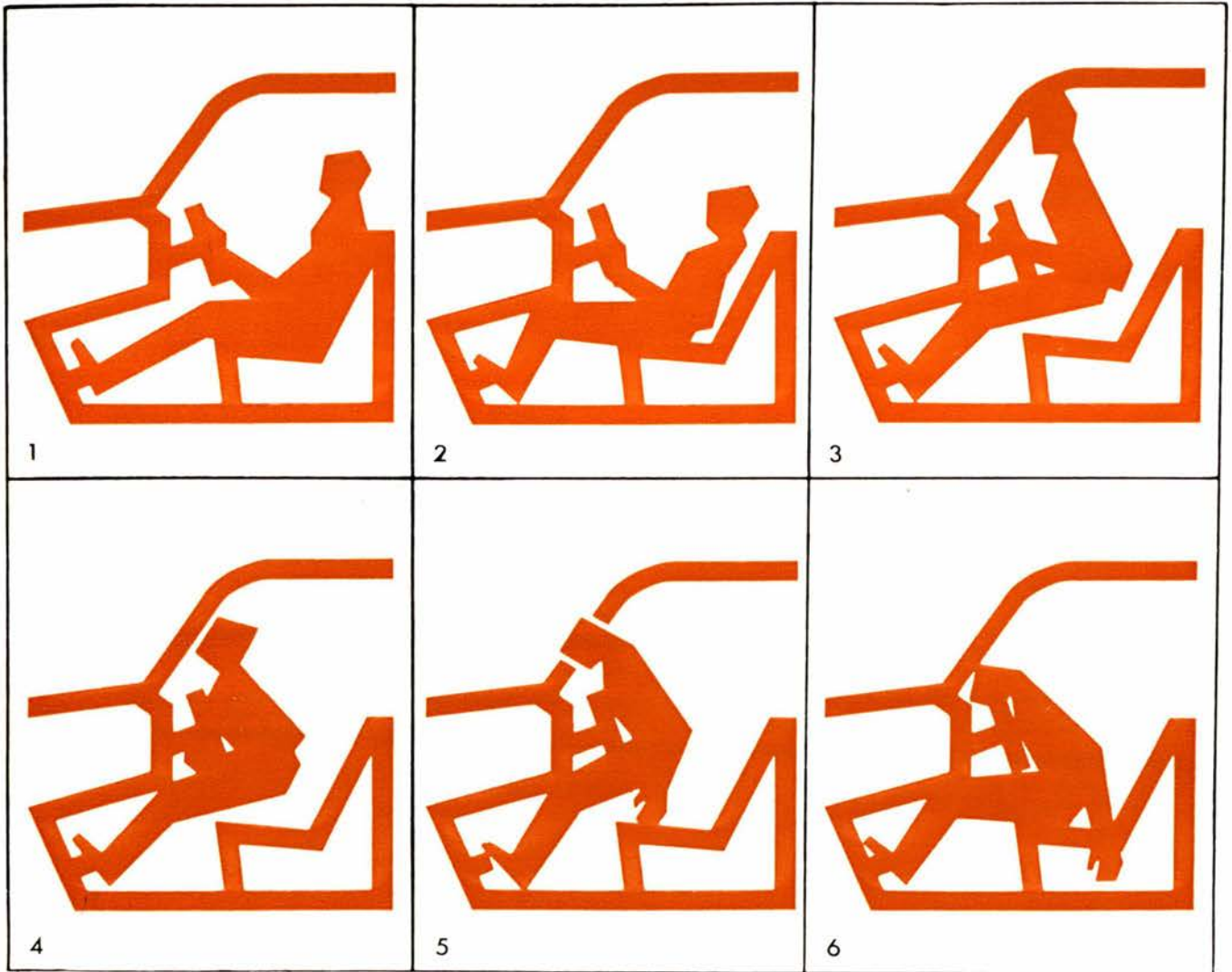
Figure 1. The movements of a driver involved in a head-on collision resulting in a sequence of impacts of knees, head and trunk — responsible for a multiplicity of injuries.

to leave their vehicle, mainly because of head injuries, and less frequently from being trapped within the wreckage.

There were three types of car collisions in this occupant fatality study and they divided themselves into almost equal proportions –

1. The single vehicle accident, when for various reasons the car left the road.
2. Car/car collisions.
3. Car/lorry collisions.

When a car leaves the road, the mechanism of injury depends on what happens next. If it overturns or goes into a roadside ditch or down a steep embankment, the occupants are thrown about and the projectile pattern of injury predominates. If the car hits a bridge abutment on a motorway, or the trunk of a large roadside tree, a telegraph pole, or a solid roadside lamp standard, deformation of the passenger compartment may be the major mechanism. Roadside design has yet to make its contribution to road safety. (Figure 2).

In car/car collisions, the projectile mechanism of injury predominates.

In car/lorry collisions, it is the deformation of the passenger compartment of the car or its penetration that results in severe injuries or death to the occupants of the car, with very rare involvement of the lorry driver or his mate. (Figure 3).

From the evidence of our current research, it is becoming increasingly evident that motorways, and roads linking motorways, are carrying increasing numbers of lorries with a proportional incidence of car/lorry collisions. In our M.1 studies between 1959 and 1962, of 51 car occupant deaths, 23 followed car/lorry collisions. In our current 1963/1965 studies, there are already 71 car occupant deaths and 42 resulted from car/lorry collisions.

As we see this problem, little can be achieved in the prevention of these collisions, other than the strict segregation of these two types of vehicles, or better still, as is the law in South Africa, of returning long distance heavy freight transport to railways.

We may now weigh up the present risks of serious injuries and deaths to road users. Taking the 100,000 serious injuries, with their 8000 deaths in England and Wales last year, in a population of 50 millions, there is a risk for all road users of 500 to 1 each year. That

a third were car occupants puts their risk each year at 1500 to 1. If we consider the life of a road user at a conservative 50 years, the odds of serious injury or death on the road in a lifetime are 10 to 1 for all road users and 30 to 1 for car occupants, and the latter odds are shortening. Expressed in another way, and more suitable for the purpose of this symposium – *Motor vehicle accidents are above all a source of 'untimely' deaths*. In 1964, in the United States, their motor vehicle fatalities bore the following relation to deaths from *all causes* –

| Ages		
1 to 4 years	10 per cent of all deaths.
5 to 14 years	19 per cent of all deaths.
15 to 24 years	38 per cent of all deaths.
25 to 44 years	11 per cent of all deaths.
45 to 64 years	2 per cent of all deaths.
65 years and over	less than 1 per cent.

Survival from serious injuries, through modern advances in treatment, has increased the incidence of permanent and often grave disablement. Surgery is not able to restore the function of tissues totally destroyed. The incidence of cerebral cripples, paraplegics and serious permanent loco motor diabilities has increased by our ability to save more lives.

Having briefly reviewed the mechanism of these severe injuries allows us to turn now to consideration of greater road user protection.

With pedestrians none can be offered and very little to the relatively unprotected riders of two-wheeled vehicles, other than the provision of pedestrian precincts and the segregation of two-wheeled vehicles from heavier traffic. This is partly, but not entirely, a matter of road design. Research directed at pedestrians has been slight relative to their proportion of the total traffic accident fatalities, but studies have shown that the ratio of fatalities to non-fatal injuries is substantially higher for pedestrians than for car occupants. With car occupants, protection against injury is now available and more can be provided. But we need to choose pedestrian precincts, and where they are provided, to use them. We need to insist on the provision of better roads; we need to choose safe vehicles and safety features in those vehicles and always use and maintain them. All could be achieved if the public demand was strong enough, and public demand and human behaviour are, in this context, inseparable. It is really up to us to develop the safety approach to road transport that we have for trains, ships and planes.

Figure 2. Two lorries travelling abreast and in the same direction, touched each other, got out of control and each crashed against large roadside trees, one driver being fatally injured and the other seriously injured.
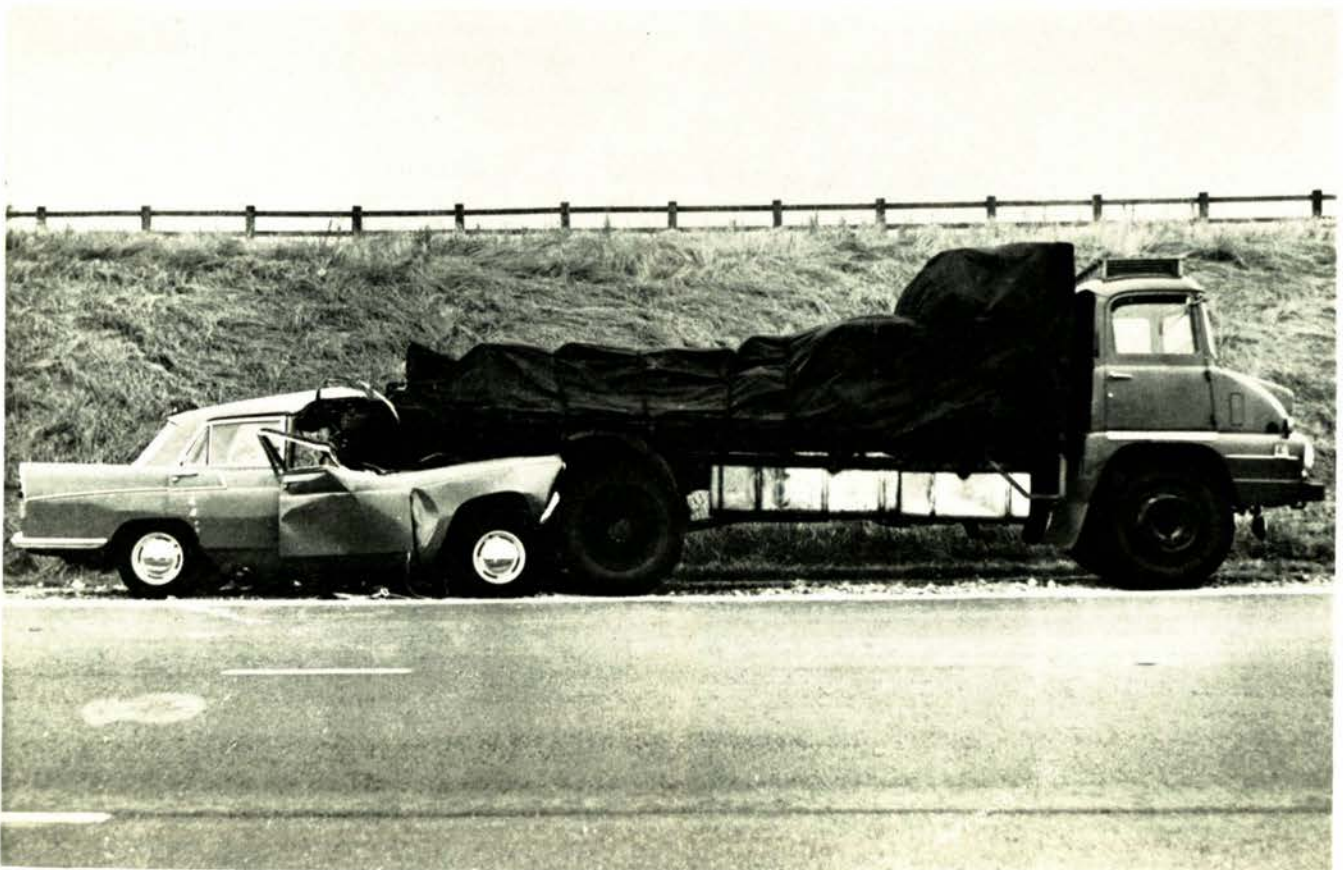
Figure 3. A very common type of fatal collision, particularly on motorways, between cars and stationary lorries – less frequent between cars and slow-moving lorries.

Car Occupant Protection

The Road Research Laboratory estimates that the constant wearing of restraining harness would result in a 70 per cent decrease in serious injuries to car occupants. American research estimates a reduction of 60 per cent in car occupant fatalities, our own Group puts this latter figure at around 50 per cent. Yet safety belts are not accepted by the vast majority of car occupants and when installed, are not constantly used. But they are as important in the prevention of the projectile pattern of occupant injuries as are the brakes of a car in the prevention of road collisions. In simple terms, safety belts are the occupants' personal braking system. They can prevent dangerous degrees of movement of both trunk and pelvis. For this purpose the diagonal component of the belt should fit as closely as trouser braces and the pelvic strap as closely as a trouser belt, worn in the modern 'hipster' fashion. Figure 4 shows the way they should not be worn. The driver was killed in a frontal collision in an intact passenger compartment. The loosely worn belt did not prevent his chest impacting the steering assembly.

At the request of the Ministry of Transport, our Research Group has investigated fatal injuries to occupants thought to be wearing safety belts at the time of their crash. Generally, though belts were in the car, they were not being worn. We have encountered only four fatalities of the projectile pattern in safety belt wearers. The one already noted with the lap and diagonal belt combination, and three others all wearing single diagonal belts. In these three, doors flew open, the cars overturned, and the belt wearer slipped out of the belt. Figure 5 shows the reconstruction of one fatality, the other two were crushed by their overturned cars.

In our studies of around 200 other fatal car occupant 'projectile' types of injuries, not one was wearing a safety belt at the time of his crash, yet had they been doing so their lives would, in our view, have been saved and many would have suffered no injury. Without any doubt, safety belts are the best protection against injury car occupants now have, or are ever likely to have, though their design can be, and indeed has been improved, by building the seat and its belt as one unit, as shown in Figure 6.

The seat structure is solid and firmly fixed to the floor, yet adjustable for comfort and easy access to the car's controls. The lap component is a fixed unit by the design of its side attachments, and goes around the bony pelvis; the diagonal component is on an inertia reel and fits over the middle of the clavicle and crosses the middle of the sternum. Thus close and correct fitting and comfort of both are easy to adjust. The tubular steel framework of this seat offers a protection against deformation injuries, particularly from side impacts, and the head restraint gives protection against hyper-extension neck injuries from rear end collisions.

Once the function, purpose and proper use of seat belts are understood by car users, then their all important safety education has commenced.

Car users should next appreciate that the belt material will stretch and the anchorage of the seat in the seat-belt combination will give to a degree, depending upon the forces of deceleration in severe crashes. They should then turn their attention to the space allowed in the car's design for this stretch or 'give' – that is the distance between their knees and the parcel cupboard, their heads and the junction of the roof and windscreen and the windscreen, the distance between their trunk and the facia panel, and pay some regard to protruding instruments that can be dangerous, on the dash and the position of those instruments. They should next examine the lay-out of the steering column and relate its design to the risks of its backward displacement following the common frontal collisions, as shown in Figure 7. They should enquire into the energy absorbing properties of the steering wheel, examine the door locks for anti-burst features, for ejection out of cars, should they forget to put on their safety belts and wear them correctly, increases the risk of serious and fatal injuries fourfold.

All these features should be, to a safety conscious purchaser, of much greater value for money than the eye-catching gimmicks of car stylists. But we need to choose safety features in vehicles and this is undoubtedly the most powerful way to have them incorporated in future vehicle design. It is really up to us to bring about a radical change in the present approach to car design.

Medicine's main objective is to prevent both injuries and diseases, and next to prevent permanent disablement and death from either cause. We have succeeded brilliantly with the infectious diseases in saving young lives; now road accidents have become
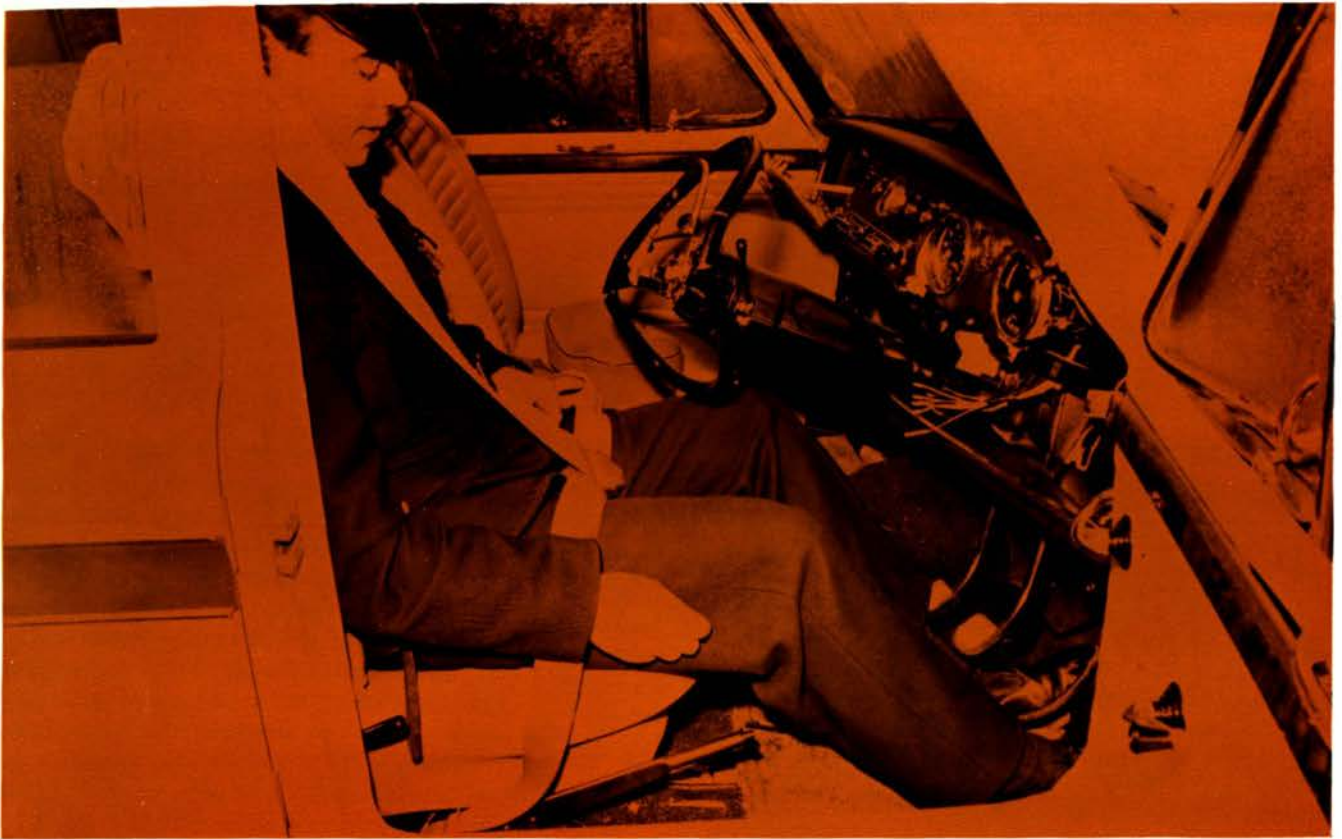
Figure 4. This belt is of the approved lap and diagonal type, but was worn much too loosely with fatal results to its driver after a head-on collision. *(The illustration does not show the actual driver).*

Figure 5. The single diagonal belt gives good protection, but if doors fly open its wearer can be partly ejected and catch his neck with resulting fatal or very serious neck injury.
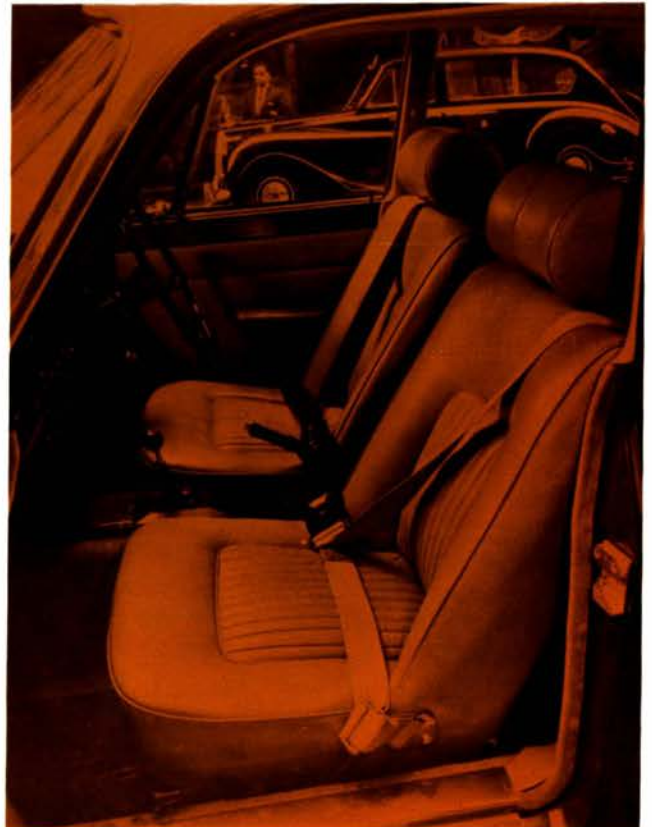
Figure 6. The fixed seat combining bolt and head rest. The belts are as they would be worn, but when out of use retract on an inertia reel into the top of the seat, and are then no encumbrance when not in use.
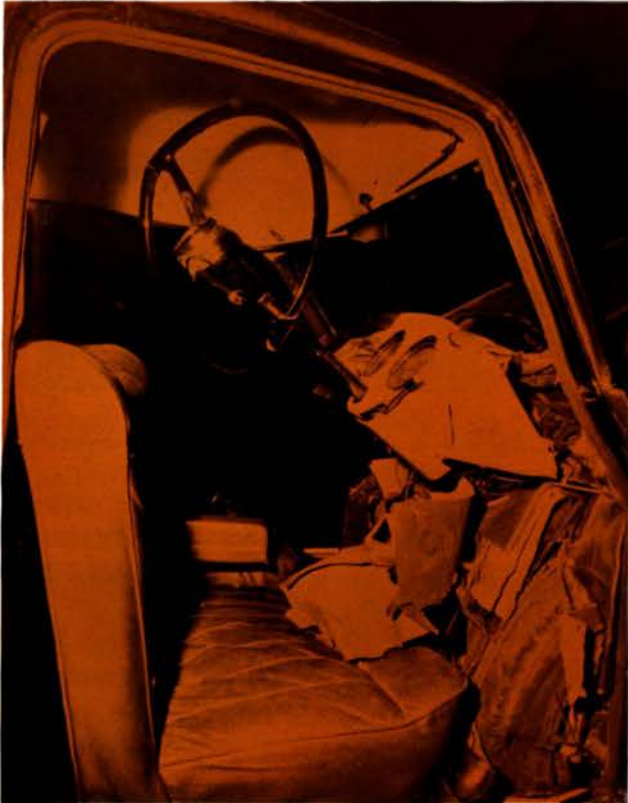
Figure 7. Following a severe frontal collision, the steering column of this car was displaced upwards and backwards. The driver's seat moved forward and his head was fatally crushed between the wheel and the car's roof.

our number one public health problem. Through more research we should seek to understand the background of these tragedies, and by conveying understanding, to speed the technical improvements and cultural attitudes that will lessen future tragedies.

Cancer Immunity

Dr David Long

UNTREATED cancer of all types is progressive and fatal, but the rate of progress of any one type of tumour varies from patient to patient even though the tumours are histologically similar. In other words, patients resist the spread and development of cancer in varying degrees. In recent years the importance of immunological factors in this 'host-resistance' to tumours has been increasingly recognised.[1] One stimulating hypothesis is that immunologically competent people recognise and destroy spontaneously arising malignant cells in a manner analogous to graft rejection.[2] Such a thesis, if proved, opens up possibilities of measuring immunological competence and quantitating it; of dividing susceptible from resistant people *before* they develop malignant disease, and of altering the immunological competence of patients both prophylactically and therapeutically. For the purposes of this paper the potential role of immunology in the prevention and treatment of cancer will be considered with particular reference to people under 45 years of age; with this age restriction, imposed by the organisers of the symposium, particular attention is paid to the possibilities of prevention.

In order to discuss immunity to cancer, it is essential first to define immunity and its component parts and then to consider their natural variation in health and disease. The quality of the data will depend on the quality of the methods used to obtain it. These have been described elsewhere[3,4,5] and are primarily of interest to those concerned with esoteric immunological technicalities.

Definition of Immunity

When protein antigens, such as diphtheria toxoid, are injected into guinea-pigs, the animals undergo a complex series of changes designed to neutralise and eliminate toxoid. These changes can be divided into allergic and non-allergic components. The allergic components are further divided into immediate (Arthus-type) reactions and delayed (tuberculin-type) reactions.[4,5,6] The latter provides the first detectable stage of the immunological response of the animal to diphtheria toxoid and is associated with an ability to localise ^{131}I-labelled toxoid at the site of the injection.[5] The former – immediate (Arthus-type) reaction – is associated with the appearance of antitoxin in serum and increases in size, as the level of circulating antitoxin rises, until it fuses with and masks the latter.[1] In a hyperimmune guinea-pig the residual damage that follows intradermal injection of diphtheria toxin is due largely to hypersensitivity to toxin. The direct toxicity of the toxin contributes relatively little.[1] (Figure 1.) The methods used in these experiments have shown that the essential part of the classic primary immune response of Glenny and his colleagues,[7,8,9]
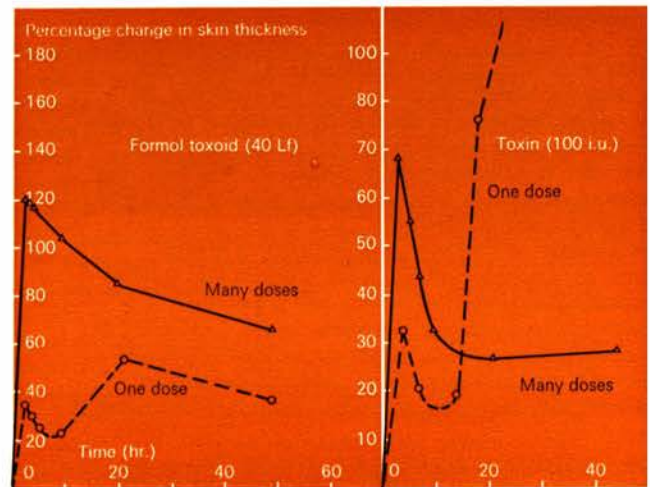
Figure 1. Guinea-pigs immunized with one or many doses of APT. Response to intradermal toxoid and toxin.

is the development of the delayed allergic response and that this may, or may not, be associated with the presence of detectable levels of antitoxin in the serum.* As pointed out above, once the delayed allergic response has developed, the antigen can be localised and this may be a necessary preliminary to the major synthesis of antitoxin known as the 'secondary response'. But, curiously enough, in guinea-pigs with very large quantities of antitoxin in their blood the removal of ^{131}I-labelled toxoid from the skin is hastened.*

If we assume that immunological behaviour in man is analogous to immunological behaviour in guinea-pigs and that immunological recognition of tumour cells is analogous to immunological recognition of diphtheria toxoid, a deduction of the greatest fundamental importance can be made which will explain much that is disappointing in attempts dating from Ehrlich until the present time to control cancer by immunological means.

From what has been said above it is clear that the immunological response is divided into two parts: the first to develop, the delayed allergic response, will tend to localise and destroy, and the second phase, with the formation of circulating antibody, will tend to spread malignant cells; it may also decrease the intensity of the delayed allergic response,* thus further reducing its cytotoxic action on malignant cells. Thus, in terms of the resistance of the host of cancer the delayed allergic response is likely to be beneficial and circulating antibody to be harmful.

The assumption will be made, for the purposes of this paper, that this deduction is true. From this point onwards our hypothesis becomes that immunological resistance to cancer is confined to the delayed allergic response and that all subsequent stages of the immune response are harmful.

The Delayed Allergic Response
The delayed allergic response is not only important because it is the essential first step in the immunological response to an antigen. In some infections where the antigenicity of the invading organism is low, for instance in tuberculosis, it may be the major, if not the only, immune defence mechanism by which the body can resist the disease. It can be passively transferred from one guinea-pig to another with immune lymphocytes but not with immune serum. The inflammatory response associated with it can be depressed by steroids of the cortisone group but not by antihistamines.[10]

The Delayed Allergic Response v The Homograft Reaction
As stated in the introduction, Burnet has postulated that the homograft immunity is a natural defence mechanism that enables immunologically competent people to recognise and destroy spontaneously arising malignant cells and that the accelerating rise with age in the incidence of malignant disease is linked with the progressive loss of capacity to initiate new immunological reactions that occurs in advancing age.[2]

The delayed allergic response and homograft immunity have a very close analogy to each other,[11] indeed at first sight it might appear pedantic, particularly in a paper prepared for a non-specialised audience, to distinguish between these two types of cellular immunity. But an attempt will be made to show that

*Unpublished data from the author.

in the study of cancer immunity this distinction is of great fundamental and practical importance.

As Medawar has pointed out in his Croonian lecture, the homograft reaction 'is known to occur in monkeys, apes, and men; in rabbits, rats, mice, guinea-pigs, dogs and (with a qualification to be mentioned later) hamsters; in sheep and cattle, chickens, ducks and turkeys; and in lizards, amphibians (including urodeles) and goldfish.[11] The homograft reaction is therefore of great antiquity – certainly coeval with, and quite possibly more ancient than, the kind of immunological reaction that depends upon the formation of humoral antibodies. The homograft reaction, in the form in which I shall consider it, is mediated not through humoral antibodies but through activated blood-borne cells. Yet no one now doubts that the homograft reaction is immunological in character.' But the delayed allergic response in its classic form does not occur in such a broad range of species but only in man, monkey and guinea-pig. Although there is a phase of 'cellular immunity' in other species it is in these species alone that the inflammatory reaction associated with the cellular response reaches its full potential for localisation and presumably destruction of antigens. But linked with this enhanced capacity to react and produce the classic delayed allergic response is an inability to synthesise ascorbic acid and a resistance to the katabolic action of cortisone. Moreover, these three separate phenomena are closely inter-related.[12]

If the delayed allergic response is the basic immunological defence mechanism against cancer and this response reaches its peak of development in man, monkey and guinea-pig, these species should have a lower natural incidence of cancer than other species and should be more resistant to the actions of carcinogens. In short, the incidence is lower and their resistance is greater; this subject is considered more fully later.

The Normal Variation in the Delayed Allergic Response
If guinea-pigs of the Hartley strain of comparable age and size and consisting of equal numbers of males and females are injected subcutaneously with a small dose of diphtheria toxoid and tested, one month later, for their capacity to produce a delayed allergic response and this process of immunisation and testing is repeated, it soon becomes obvious that, immunologically speaking, some guinea-pigs are 'rapid starters' and some 'slow starters'. A few produce a marked delayed allergic response after a single dose of antigen, a few fail to produce one even after several doses of antigen. Between these extremes are the varying degrees of response that might be anticipated on general biological principles, the majority starting around the centre of the response curve and the numbers fading uniformly to each extreme. If this degree of variation occurs in the closely interbred Hartley strain of albino guinea-pigs at the National Institute for Medical Research, it is reasonable to assume that at least as great a variation occurs under natural conditions in the other species that produce the classic delayed allergic response, namely man and monkey. It is noteworthy also that guinea-pigs that produce a delayed allergic response to a single dose of antigen rapidly complete their full immunological response to reach quickly a maximum titre of circulating antibodies. Slow starters may take many doses of antigen and many months to achieve comparable levels.

There is not only variation *between* the responses of individual animals, there are also variations *within* the responses of individual animals and these are linked with their stage of development. This is not only true of the delayed allergic response and subsequent immunological behaviour of guinea-pigs in response to diphtheria toxoid, but is probably true of the immunological response of most species to most antigens. For instance, Medawar and others (see Proc. Roy. Soc. B. (1956) **146**, 1, A discussion of immunological tolerance) have shown that antigens injected into the foetus produce a state of tolerance. Tolerance has been defined as 'a state of immunological non-reactivity that is brought about by exposing animals to antigenic stimuli before their immunological faculties have become mature'.[11] But it is also known that a similar state of specific immunological paralysis can be produced in mature animals by injecting a massive excess of antigen. It is probable in both cases that the essential requirement is a gross excess of antigen in relation to the number of immunologically competent cells. This hypothesis is supported by the fact that the human foetus produces antibody against rubella, an infection associated with the liberation of relatively small amounts of antigen, and also by the fact that if in the mature animal the number of immunologically competent cells is decreased by 'X' irradiation or by the use of radiomimetic drugs, antimetabolites or corticosteroids, the dose of antigen required to produce immunological paralysis is proportionally reduced. In theory, immunological tolerance to grafted tissues might be produced in man by such means and some authorities believe that it is. Of more direct concern to the problem of cancer immunity is whether immunological tolerance to malignant tumours might occur. Much has been said about antigenic loss of cancer cells leading to failure of immunological recognition of the tumour by the host[13,14,15] but the alternative hypothesis that malignant cells may produce immunological tolerance by decreasing the cellular immune response of the host has not, to my knowledge, been put forward, although Pulvertaft used to show a film of malignant cells phagocytosing lymphocytes and it is known that malignant cells readily metabolise globulins. Clearly this is no more than a speculation but it is at least as attractive as some of the immunological hypotheses advanced at the present time to explain the diminished immune cellular response seen in patients with malignant disease. But after this rather lengthy diversion on the reason for the diminished capacity of new born animals to produce a delayed allergic response, the other causes of variation in the response of individual animals must be considered.

During the phase of growth when protein anabolism is maximal there is a maximal hypersensitivity response of the delayed allergic type to antigens. This capacity fades with the slow katabolic process of old age.[2] This relationship between the intensity of the delayed allergic response and anabolism and katabolism of protein has been studied in some detail in guinea-pigs by my colleagues and myself. Anything that decreases the synthesis of protein depresses the delayed allergic response. Some years ago the hypothesis was advanced that the intensity of the delayed allergic response was proportional to the –SH content of the tissues.[16,17,18] Therefore ethionine, the anti-metabolite for methionine, a precursor of glutathione, was given to guinea-pigs.

It profoundly depressed the delayed allergic response to tuberculin. Later, by chance, a naturally occurring protein deficiency syndrome grossly interfered with attempts to assay an anti-allergic substance that Martin and I had found in peanut oil and in egg yolk.[19] This led us to further experiments which showed that a deficiency of essential aminoacids, or indeed starvation, has a similar, though less marked effect than ethionine. Throughout these experiments the basic hypothesis that the intensity of the delayed allergic response depends on the –SH content of the tissues has remained intact and much indirect evidence in support of it has been obtained.[17] It is noteworthy that the synthesis of new steroids with greater potency* than cortisone has been achieved at a cost of increased interference with protein synthesis. Thus, unfortunately, it is now possible even in the case of the 'cortisone-resistant' human species,[12] at least in infancy, to prevent growth with modern synthetic steroids. This is a very serious complication of such therapy.

If it is assumed that the delayed allergic response provides a defence mechanism against malignant disease, and if the analogy between guinea-pig and man is sound, anything that increased protein anabolism or the –SH content of the tissues should increase resistance to malignant disease – whereas katabolism of protein and wasting should hasten the disease process by reducing natural immunological resistance.

The potential importance of such enhancement of the natural immunological resistance of the host is very great indeed because it is non-specific, that is to say it would enhance resistance to *all* antigenic tumours, whether they have common antigens or not.

Certain virus diseases, notably measles, depress sensitivity to tuberculin, the classic example of the delayed allergic response[20,21,22] and this has led to speculation that oncogenic viruses might have a similar effect, thus decreasing the delayed allergic component of immunological resistance of the host to his tumour.

Whether because of katabolism of protein or because of oncogenic viruses behaving as immunosuppressants or for other reasons of which we are ignorant, none can dispute that patients with malignant disease have a decreased delayed allergic response and slowly reject grafted tissue (both malignant and non-malignant).[23,24,25,26,27]

It would be of great interest to know whether the –SH content of the tissues of patients with malignant disease is low and whether, if it can be raised by stimulating anabolism of protein or by drug therapy, the delayed allergic response is increased and with it resistance to malignant disease. It would also be interesting to know whether the capacity to produce a delayed allergic response is reduced *before* the patient develops malignant disease. Are they, in fact, analogous to the immunological 'non-starter' guinea-pigs mentioned above? Do patients develop malignant disease because their immune cellular defence mechanism is not fully competent to recognise and destroy spontaneously arising tumours, or does the development of the tumour cause this incompetence?

It is known that many cytostatic drugs decrease the delayed allergic response and are classified under the vague and often

*By 'potency' I do not mean increased activity per unit weight, but a greater range of effect than can be achieved with maximal doses of cortisone.

misleading term of 'immunosuppressives', but there is little data on the immunological behaviour of patients *after* cytostatic drugs are withheld. Many years ago, Miles and I showed that cortisone depressed the tuberculin response in guinea-pigs and this was followed by a 'rebound phenomenon' in which sensitivity to tuberculin was increased.[10] A similar 'rebound phenomenon' has been found with cytostatic drugs. One of the most interesting has been the recent paper by Chanmougan and Schwartz showing that if 6-mercaptopurine is given to rabbits which are then rested without drug treatment for a period of five days, a hyperimmune response was obtained to bovine gamma globulin.[28]

Rebound phenomena following immunosuppressant therapy have important implications in graft control, in the treatment of auto-immune diseases with cytostatic drugs and in the treatment of malignant disease. Clearly in the latter case if cytostatic drugs could be used in short courses to cause first and directly maximal tumour damage to the primary tumour and later and indirectly maximal increase in intensity of the delayed allergic response around secondary deposits, their effectiveness in therapy might be increased.

The Delayed Allergic Response in Relation to Cancer

The hypothesis to be considered in more detail is that the delayed allergic response provides the main immunological defence mechanism against cancer. Additional evidence in support of this will now be considered under five main headings.

1. The significance of the 'cortisone-resistant species'

Man, monkey and guinea-pig, as mentioned earlier in this paper, are the only species with the capacity to produce the classic delayed allergic response of the tuberculin type. In these species the ability to localise antigens, which marks the first stage of immunological experience, is associated with a marked inflammatory response leading to local necrosis of tissue.

These species are alone in being unable to synthesize ascorbic acid and in being resistant to the katabolic effects of cortisone. Moreover, these separate features are interrelated.[12]

If the delayed allergic response, as an additional component of cellular immunity in 'cortisone resistant' species, provides the main immunological defence mechanism of the host against tumours it follows that man, monkey and guinea-pig should have a lower natural incidence of malignant disease than 'cortisone-sensitive' species and should be more resistant to carcinogens and to the induction of virus induced tumours.

Monkeys
Very little work has been done on this subject but fortunately the Russian worker, B. A. Lapin, has made studies in this field of the greatest importance and has reviewed them in English in a recent paper.[29] This paper should be read in full, but in brief Lapin makes several points:

1. Tumours are rare in primates. [30,31,32]
2. He states: 'The overwhelming majority of attempts at reproducing tumours in these animals end in failure. They may be subdivided into those associated with the use of chemical carcinogens, hormonal preparations, and with the use of natural radioactive material and artificial radioactive isotopes'.
3. Resistance of monkeys to virus induced tumours is high though they can be readily induced in the new born.
4. Monkey tumours commonly regress and are replaced by fibrous tissue. Lapin states 'the regression of the neoplasm, having initially the structure of a malignant tumour, is of interest and needs special investigation.'

Lapin's work has been carried out under almost ideal conditions, the monkeys being given a high degree of freedom and many being allowed to complete their life span with minimal interference from man. Few species under natural conditions live long enough to have a high incidence of cancer but in most species, if life is prolonged by the protection of man, the incidence of cancer is very high, e.g. rats, mice and rabbits. But Lapin has shown this is not true for primates.

Guinea-pigs
The natural incidence of malignant disease in guinea-pigs in the experimental laboratory is very low. In my own experience of many thousands of guinea-pigs I have seen one malignant hepatoma arising in the liver of a guinea-pig which had been grossly damaged by a naturally occurring Kwashiorkor-like syndrome that caused severe liver damage.

In a review of the literature, Leader found only 21 cases of spontaneous tumours in guinea-pigs.[33] No malignant growths were detected in 15,000 guinea-pigs at the Bettsville Agricultural Station of the United States Department of Agriculture.[34]

Guinea-pigs are known to be very resistant to the action of carcinogenic agents. Russell and Ortega state: 'Because of difficulties observed in inducing tumours in guinea-pigs with carcinogenic substances, these animals have not been used so frequently in cancer research as rats and mice. The relatively poor response of guinea-pigs to carcinogenic stimulation has been attributed to an inherent species resistance'.[35] But they and other workers showed that methylcholanthrene produced cancer in this species of animal.[36,37]

Man

The graph in Figure 2, kindly provided by Stephen Israel, Statistician to the Office of Health Economics, should I suggest be considered together with a quotation from a recent paper by Sir Macfarlane Burnet who writes:

'At the human and practical level it may be that the most important effect of immunological processes is to be seen in the shape of the curve of the age incidence of malignant disease. The peak is in early childhood, which would correspond to malignant disease initiated in the perinatal period of immunological inadequacy, and the accelerating rise with age after middle life may be in part associated with the progressive loss of capacity to initiate new immunological reactions with advancing age'.[2]

To these general observations might be added the additional point that the natural incidence of malignant disease in man is low when compared with 'cortisone-sensitive species' in spite of his artificially vastly extended life span. Naturally, attempts to produce cancer in man are few in number, but important work has been carried out by Southam and his colleagues. [38,23,25,27] This fully justifies Southam's recent conclusions: 'The question of immunological reactions against autochthonous human cancer was

investigated using the techniques of auto-transplantation, homotransplantation, serology and skin tests. Due to the biological complexity of cancer and the restrictions of clinical research, the data seldom permit unequivocal conclusions but all of the results are consistent with the hypothesis that there are host defences against autochthonous cancer and that such defences may act upon cancer-specific antigens and may work through cellular mechanisms.'[27]
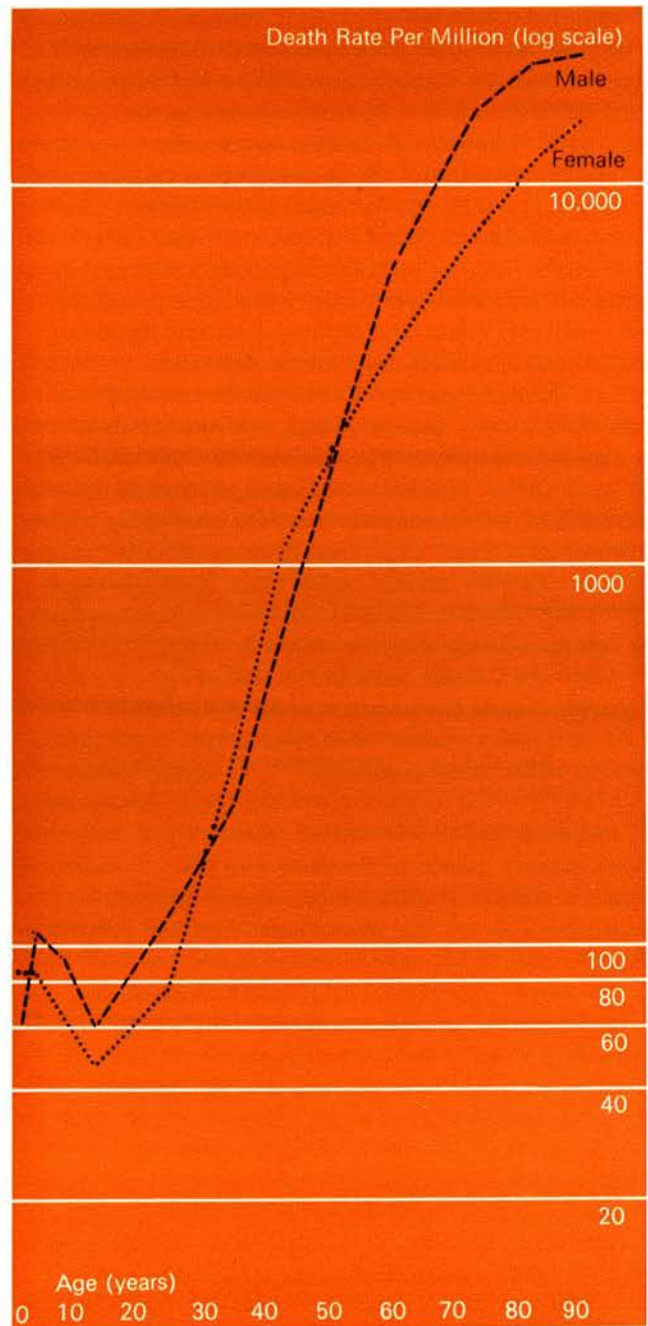
Figure 2. Malignant Neoplasms. Death rate per million living. England and Wales 1964.

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2. The site of the tumour

If the capacity to produce a delayed allergic response is correlated with the capacity to recognise and destroy tumours, there should be a marked variation in the immunological resistance of the host to tumours arising in different parts of the body. Many years ago it was found* that if 0·25 Lf of alum precipitated diphtheria toxoid was injected intradermally into one group of Hartley guinea-pigs, subcutaneously into a second group, intramuscularly into a third group and intravenously into a fourth group and the capacity to produce a delayed allergic response to diphtheria toxoid was measured one month later by the method of Long and Miles [10], that very large and statistically highly significant differences in response were obtained. The delayed allergic response to animals immunised intradermally or subcutaneously was very great and the response of animals immunised intramuscularly or intravenously very small. On this basis, if the analogy is valid, host resistance to tumours depending on the delayed allergic response would be much greater when the tumour arose in the skin or subcutaneous tissues than when it arose in muscle or in the circulatory system. This deduction is compatible with clinical experience.

3. The rate of growth of tumours

The work already quoted of Southam and his colleagues in man and routine experimental methods in animals have shown that transplanted tumours are handled by the host like other transplanted tissue and induce the classic transplantation immune response, but if the number of malignant cells injected is large enough and growing with sufficient rapidity, the rate of growth of tumour combined with its mass are too great for the immunological defences of the animal and the tumour becomes established. It follows that with rapidly growing tumours immunological recognition, to be effective, would have to occur at an early stage when there are few cells to be destroyed and that the 'immunological slow starters' mentioned earlier in this lecture might never contribute effectively to the defence of the host. In such a case the destruction or elimination of the mass of the primary tumour with cytostatic drugs, or by surgery, might be combined with ways of boosting the immunological defences of the host to destroy the smaller numbers

*Unpublished data from the author.

of malignant cells present in secondary deposits in the early stages of metastasis.

4. Cytostatic compounds and the rebound phenomena

Most cytostatic drugs are also immuno-depressive drugs so that when used in the treatment of malignant disease they may have two actions. They destroy the malignant cells which is beneficial to the host, but they may also diminish the cellular immune response which has been postulated to be a basic defence mechanism, if this hypothesis is valid such an effect will be harmful.

Miles and I showed that a single injection of cortisone acetate depressed the delayed allergic response in the guinea-pig but that some days later a rebound phenomena occurred and the capacity to produce a delayed allergic response was enhanced.[10] Later experiments showed that the delayed allergic response could be intensified immediately with insulin but that within hours a rebound phenomena occurred and the delayed allergic response was greatly reduced.[16]

Recently, Chanmougan and Schwartz have shown that if rabbits are treated with 6-mercaptopurine and then rested for five days they produce a hyperimmune response to antigens.[28] In other words, there is at least a theoretical possibility that cytostatic drugs could be given in short courses in maximal dosage combined, if need be, with surgical treatment or with local X-irradiation designed to diminish tumour mass with the hope that once this treatment was stopped the resulting rebound phenomena would be associated with a hyperimmune delayed allergic response associated with increased host resistance. The good clinical response of Burkitt's lymphoma and of chorionepithelioma to short courses of drugs might be due in part to such a mechanism.

5. Debility

There is no doubt in guinea-pigs that anabolism of protein increases the capacity to produce a delayed allergic response and that katabolism decreases it.[17] If the analogy is valid for man and a way could be found to induce anabolism of protein in man, the resistance to tumours would be enhanced. It is relatively easy to produce anabolism of protein in rats with a variety of anabolic steroids, but man is resistant to such effects. If a drug could be found which was

really effective in man it would be important to study its effect on the immunological resistance of man to cancer.

Conclusions

This Symposium is entitled *Alive to Forty-Five*. The intention of this paper is to outline 'recent progress and future prospects in the prevention of premature deaths from cancer'. With these instructions in mind it is necessary to leave speculation and to state what might be done to reduce the number of deaths from cancer in youth and middle age.

Analysis of Immunological Competence of patients before and after they develop malignant disease

If our hypothesis is correct that the incidence of malignant disease in individuals is correlated with their capacity to produce a delayed allergic response, then if patients under forty-five years of age were injected with a standard antigen and this capacity was quantitated, it would be possible to select the 'immunological non-starters' or poor starters. In other words, to detect before they develop malignant disease, those who are most susceptible to it. For instance, if known heavy smokers could be classified in terms of their capacity to produce a delayed allergic response and 'immunological non-starters' proved to develop a high incidence of cancer of the lung, it might be possible to prevent them from smoking and to be more lenient with the immunologically resistant group. But if immunological incompetence could be detected, what might be done to protect them from cancer in general, quite apart from that due to smoking, and what might be done to help those in whom a diagnosis of cancer had already been made?

Ways of increasing the delayed allergic response

1. Specific means

Tumour Antigens

If tumour antigens could be isolated and injected intradermally a high degree of delayed allergic sensitivity could almost certainly be achieved in people capable of responding. Based on the analogy with guinea-pigs even 'late starters' would eventually acquire a significant degree of immunological resistance. But the chief objection to this approach is that the large number of tumour specific antigens makes it impractical even if it could be shown to be effective.

Transfer of Immunity

In theory, lymphocytes from an animal immunised against a tumour could be injected into animals bearing that tumour or, alternatively, the capacity to react against the tumour could be transferred from these immune lymphocytes to the lymphocytes of the tumour bearing animal with the transfer factor of Sherwood Lawrence or with RNA obtained from these immunised cells.[39] The difficulty is that whole lymphocytes or component parts are likely themselves to be antigenic and, if so, their action will be short-lived. Advances in this type of therapy are likely to have to await advances in the control of graft rejection – the problem being virtually that of grafting a new immunological defence system into the host. Another problem is the large number of tumour specific antigens to which the grafted immunological system would have to respond.

A good deal of work on the effect of immune lymphocytes against cancer has been done in mice and rats.[41,42,43,44,45,46] *

2. Non-specific means

Stimulation of the reticular endothelial system

Oleic acid,[48] zymosan,[49,50] B.C.G. vaccine[51] and more recently a vaccine made from C. parvum[52] have been used in animals to increase cellular immunity to cancer.

Enhancement of already existing delayed allergic responses

Sensitivity to tuberculin can be altered very greatly and very rapidly in guinea-pigs by non-specific means.[12] Thus, anabolism of protein, the injection of insulin, the injection of –SH compounds, the injection of small doses of thyroxine over long periods of time, all increase the intensity of long existing sensitivity to tuberculin. It is probable that anything that increases the –SH content of the tissues will increase the intensity of delayed allergic inflammation where it already exists around tumour cells.

The biochemistry of acute allergic phenomena has been studied intensively and histamine, serotonin, bradykinin and many other mediators of inflammation have each led to an extensive literature of their own. But the biochemistry of the delayed allergic response has been neglected and, in particular, in relation to ascorbic acid and glutathione metabolism.[12,17]

*This work has been reviewed by Alexander in *The Biology of Cancer*.[47]

The other aspect of this type of non-specific stimulation of the delayed allergic response that deserves further study is the rebound phenomenon referred to earlier.

Finally, it may not be too fanciful to speculate on the possibility that humans, like guinea-pigs, may produce a delayed allergic response to antigens ranging from the minimum to the grossly excessive with all intermediate ranges. It may be that those individuals who over react are destined to suffer from autoimmune disease but not from cancer and to be resistant to attempts to graft organs on to them, that those individuals who under react are susceptible to malignant disease and will produce a minimal graft immune response. If this hypothesis is true, most of us will be between these two extremes.

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Heart Disease

Dr John Hamer

THE major cardiac causes of death between the ages of 15 and 45 years are rheumatic heart disease and cardiac infarction.

Chronic rheumatic heart disease is the end result of acute rheumatic fever in childhood or adolescence. There is now good evidence that rheumatic fever is a complication of the immune response to streptococcal infection as a result of the accidental similarity from the antigenic point of view of bacterial and connective tissue proteins. There has been a striking reduction in the incidence of acute rheumatic fever since the early years of this century, due to the improvement in living conditions and the introduction of antibiotics. However, acute rheumatic fever continues to occur, and consideration is being given to immunisation against the appropriate strains of streptococcus. However, the antigens involved are compex; 50 different types of M protein have been recognised in group A streptococci, and vaccines against these factors give rise to hypersensitivity reactions, so no satisfactory method has yet been developed.

Although prompt treatment of acute rheumatism with salicylates or steroids may reduce the immediate mortality due to severe carditis, there is no evidence that treatment alters the incidence of subsequent valve disease. A patient who has had rheumatic fever is particularly liable to a recurrence, and the best way to reduce the incidence of chronic valve damage is to insist on penicillin prophylaxis to reduce the number of subsequent attacks. Oral prophylaxis with penicillin or sulphonamides has been shown to be effective, as is a monthly injection of depot penicillin.

There is no doubt that since the last war cardiac surgery has greatly improved the outlook in chronic rheumatic heart disease. The commonest valve lesion, mitral stenosis, is in many cases completely relieved by mitral valvotomy, a relatively simple operation in which the narrowed valve is split open. However, in other patients the severity of the damage to the valve, particularly calcification, or the presence of changes in other valves, prevents effective treatment in this way. Progressive ill health and premature death was the usual outcome in these patients until recently, although some complications could be prevented. For instance, bacterial endocarditis can be avoided by effective antibiotic cover for dental extraction or genito-urinary surgery, systemic embolism can be prevented by anticoagulant therapy in susceptible patients, and heart failure can be treated effectively for a time with the modern powerful diuretics.

The situation has been transformed in recent years by the introduction of the artificial heart valve. It is now possible to remove the diseased valves and replace them with a mechanical prosthesis, so restoring normal mechanical function in the heart. Very great improvement is produced by this type of surgery, although, of course, the operation is a major one. At my own hospital the surgeons have operated on over a hundred patients in this way with very satisfactory results. Because of the risk of the operation we have been treating only the very seriously ill patients in this way, and although they are greatly helped by the operation, the damage to the heart muscle that has occurred over the years cannot be corrected, and they will probably still have some trouble from this in the future. There is also some risk of clot formation on the prosthesis. The change in prognosis produced by the operation is, however, already considerable, and we expect a progressive reduction in the risk of operation in the future.

An alternative to an artificial valve is the use of a freeze dried human valve from a cadaver, or of an animal valve. This has its problems however. The mitral valve is a very complex structure and it is difficult to insert another similar valve accurately. Also the grafted valve may suffer similar degenerative changes to the natural one as years go by. I expect that the popularity race between the artificial valve and the graft will continue for many years.

A more remote possibility is the complete replacement of the heart either with a grafted heart from someone dying from disease of another organ, or by a mechanical heart. The problems of a transplanted heart are immunological, apart from the supply difficulties. The mechanical heart does not seem feasible at present as there is no way of removing the heat produced by the motor unless the power supply is external. A device relying on a compressed air line to the patient has been used but the risks of loss of power seem too great to make it practicable.

The second major cause of cardiac death in middle life is cardiac infarction. The usual cause of this condition is arteriosclerotic change in the coronary arteries with secondary thrombosis leading to a sudden loss of blood supply to the heart muscle.

Angina, of course, is produced by similar less severe changes. No single cause of coronary arteriosclerosis can be established, but there are a number of factors associated with this disease process which are probably of aetiological importance. Although all these factors can be corrected, it is clear that the changes in the coronary arteries begin in childhood, so that by the time the patient is taken ill the process is well advanced and correction of the underlying disturbances has little, if any, effect on the outlook. Routine electro-cardiograms may lead to the discovery of coronary artery disease before symptoms have occurred, but the value of treatment applied at this stage of the disease is doubtful. The main hope for the future is in the fundamental alteration of the national way of life.

Five main factors associated with coronary artery disease have been revealed by prospective studies of whole populations, the best known being that at Framingham, Mass. A *high blood cholesterol* is a simple index of the complicated changes in blood fats that occur in coronary artery disease. Some of the increase in cholesterol level may be due to a familial tendency to the disease or to a low level of physical activity. This aspect of the problem can be tackled by regular exercise, but it is not possible to alter one's choice of parents. A genetic tendency to coronary artery disease may be accumulating in the population and is not influenced by natural selection as it does not interfere with the patient's life till after the reproductive period. Drugs which lower the blood cholesterol level have a place in the treatment of patients known to have a familial abnormality of fat metabolism in whom treatment can be started before overt trouble has developed. Their value after coronary artery disease has appeared is more doubtful. *Obesity*, defined as body weight more than 20 per cent above the standard, is another factor which can be corrected. There is no doubt of the correlation with *cigarette smoking*, and the moral here is obvious. From the medical point of view the remaining two factors, *diabetes* and *hypertension*, are important as they produce no early symptoms but may be detected by routine examination. There is much mild undiagnosed diabetes in the community which can be discovered by routine urine testing, and treatment of these subjects may prevent the coronary artery complications. Similarly the prompt treatment of high blood pressure may reduce the strain on the coronary arteries.

The importance of psychological stress on the development of coronary artery disease is difficult to evaluate. Stress of this sort may affect the blood cholesterol, or produce an undue tendency to thrombosis. Although thrombosis is the main cause of the blockage of the coronary arteries in most cases there is no evidence that the conventional anticoagulant drugs have any effect on the disease.

About 20 per cent of patients with coronary artery disease die suddenly without warning, and many others have such severe damage to the heart that they die in a few hours, so it seems unlikely that it will be possible to reduce the mortality of cardiac infarction very much. In most patients who survive the first few hours of the illness the outlook is good. It cannot be over-emphasised that most patients make a complete recovery from coronary thrombosis and are able to return to their work in a few months. The group which is particularly amenable to treatment is that in which temporary electrical changes in the heart cause sudden death in a patient who would otherwise make a good recovery. The risk is chiefly confined to the first few days of the illness. Effective management of these patients requires that all patients with coronary thrombosis should be admitted to hospital as soon as possible. Careful observation may detect slight changes in the heart rhythm which gives warning of the development of more severe changes.

The main danger is the appearance of ventricular fibrillation. This disturbance prevents any effective heart beat and the patient appears dead. However, an electric shock across the chest can produce complete recovery. The patient can be kept alive by external cardiac massage and mouth to mouth breathing if these are begun within three minutes, but the electrical treatment must be used as soon as possible. Prompt treatment requires careful observation by trained persons. In many centres electronic monitoring equipment is being used to detect these disturbances automatically. Although saving a patient in this way is dramatic, the reduction in mortality by these techniques is relatively small. It is worth noting that with the greater interest in the treatment of coronary thrombosis in recent years the frequency of ventricular fibrillation has fallen, probably because of more careful general management.

Another change in cardiac rhythm, heart block, can be treated by electrical methods. In this condition

the heart rate becomes very slow, and the heart is stimulated electrically at a normal rate. The outlook in these patients is bad as there is usually serious damage to the heart muscle. Extensive cardiac infarction interferes with the action of the heart as a pump, and leads to a fall in blood pressure and a reduction in blood flow to the vital organs. The management of patients with very severe cardiac damage is unsatisfactory. The number of proposed treatments is almost equal to the number of physicians interested in the subject. Some form of artificial circulation may help to carry the patient through the acute phase of the illness, but the heart is so badly damaged in many cases that it will probably not be able to take over again.

The best approach to reducing the incidence of coronary artery disease is the application of sensible prophylaxis from early in life. The classical advice of 'moderation in all things' is still applicable.