Original Articles

Parity and Susceptibility to Cancer

Sir Peter Medawar CH FRS and Ruth Hunt

Summary

Reasons are given for supposing that the protective effect of a teenage pregnancy upon susceptibility to breast cancer is akin to a natural vaccination by fetal antigens which produce a change of state that discourages the inception and growth of tumours. Such a change of state may also be procured by the inoculation into mice of certain adult tissues with embryonic properties. They include irradiated testicular and thymic tissue. These observations are thought to hold out the distant hope of devising a protective vaccine against tumours.

Introduction

In the past two or three decades epidemiology has been the branch of medical science that has made the most important contribution to our understanding of the aetiology and prophylaxis of cancer. The subject under discussion in this paper is no exception to this generalization, for the influence of a woman's reproductive history upon her risk of contracting various forms of cancer is a matter that lends itself particularly well to epidemiological analysis.

1 Abridged version of lecture delivered by Sir Peter Medawar at Riyadh Military Hospital on 5 December 1979
2 Address for enquiries: Clinical Research Centre, Harrow, Middlesex, HA1 3UJ, UK.
A case in point is the work of Beral, Fraser & Chilvers (1978) upon parity in relation to the risk of ovarian cancer. Studies in a variety of countries with widely differing reproductive customs have demonstrated a clear negative correlation between average completed family size and mortality from ovarian cancer; the standard mortality ratio varies from one decade to another but the data illustrated by Figure 1 show how mortality from ovarian cancer in England and Wales and the USA reached a peak among the generation of women born around 1906 – the generation that was of reproductive age round the period of the great depression – a period during which fertility fell so low as to create the widespread impression that peoples of the Western world could no longer maintain themselves reproductively and were doomed therefore to extinction (Lotka 1945).

![Graph showing standardized mortality ratios from ovarian cancer in England and Wales and the USA for generations of women born at 5-year intervals between 1861 and 1931.](image)

**Figure 1.** Showing how in both England and Wales and the USA mortality from ovarian cancer reached its peak in the cohort of women who reached reproductive age during the period when fertility was lowest in the Western world (see text). (Reproduced by kind permission of Dr V. Beral and the Editors of the Lancet.)

A second example of the relationship between reproductive history and susceptibility to cancer is that which has been revealed by a multinational epidemiological survey of breast cancer led by Dr Brian MacMahon of the Harvard School of Public Health (1970). Here too it was at one time believed that there was an inverse correlation between susceptibility to breast cancer and total numbers of children born. Deeper analysis showed, however, that the really important independent variable was not the total number of children born but age of mother at the birth of her first child. The strength of the correlation is made apparent by Figure 2 (see MacMahon, Cole, Lin, Lowe, Mirra, Ravnhar, Salber, Valaoras & Yuasa, 1970).

Taking the susceptibility to cancer of childless women as a base line, the correlation diagram makes it clear that women who have their first child by or before the age of 20 have a relatively lower risk, and women who have their first children at or beyond the age of 30 a relatively higher risk of becoming victims of breast cancer.

These are among the most important epidemiological findings of the past several decades of cancer research. How are they to be explained?

Medical students and beginners inexperienced in research tend to titter cynically when they learn that endocrinologists favour an endocrinological interpretation of these findings and immunologists an immunological interpretation.
In reality such a predisposition is the most natural thing in the world: *we must seek where the light is* – no useful purpose is served by floundering around in the dark. We turn first to those areas of medical science that are already brightly lit. We ourselves are inclined to an immunological interpretation and the remainder of this paper is a summary of the evidence that justifies such an opinion.

**Anaplasia and Anti-embryo Immunity**

The case for an immunological interpretation is based upon the conjunction of two quite separate lines of evidence: the existence of (A) the phenomenon of anaplasia and on the other hand (B) the phenomenon of anti-embryo immunity.

(A) **Anaplasia:** The great German pathologists of the nineteenth century who founded the science of pathology were very much attracted by the idea that tumour cells revert in certain respects to an embryonic type (review by Medawar 1977); some indeed thought of ‘dedifferentiation’ as a defining characteristic of malignant growth. This cannot be right, however, for very many tumours continue to manufacture their characteristic differentiation products: B cell tumours may continue to manufacture immunoglobulin and thyroid tumours thyroglobulin; many epidermal tumours, moreover, often continue to keratinize. Yet in spite of evidence of this kind the notion has lingered on and today there is biochemical evidence, universally admitted to be valid, that tumours do sometimes, perhaps often, manufacture substances of which the
synthesis would normally have ceased during or by the end of fetal life. The first such substance to be discovered was CEA (carcinoembryonic antigen) (Gold & Freedman 1965). Another well-attested example is the manufacture by hepatic tumours of mice and men of alphafetoprotein (Abelev 1963). Similarities between tumour and fetal tissue have also been reported in respect of RNA transferases and the isoenzymic profiles of lactic dehydrogenases. To these may be added the discovery by Ten Feizi (Feizi et al. 1975, Feizi et al. 1979) of the occurrence in endodermal tumours of blood group precursor substances I and i. References to many of these discoveries are made in P. Alexander’s admirable review (1972) of oncofetal antigens; in Anderson & Coggin (1971); Coggin & Anderson (1974); and in Rees, Price & Baldwin (1979).

(B) Anti-embryo immunity: The second of the two lines of evidence whose conjunction forms the theoretical basis of this communication is that which relates to anti-embryo immunity: embryos are sufficiently unlike the adults into which they develop to make it possible for them to arouse an immunity reaction after injection into adults even of the same genetic composition. This immunity is directed against embryonic tissue as such, that is to say, not merely directed against the embryo as a genetically foreign body containing antigenic substances inherited from the father (such is the case with rhesus immunization). Anti-embryo immunity can therefore be aroused in mice of a single genetically uniform strain. Anti-embryo immunity is also aroused by natural pregnancies (Brawn 1970, Hellstrom & Hellstrom 1975).

Anti-embryo immunity belongs to the general class of cell-mediated immunological reactions; antibodies are exceedingly difficult to detect – just as were antibodies against tissue allografts in the early days of the study of graft rejection processes but several authors have described the formation of cytotoxic lymphocytes which are capable of reacting upon embryo cells grown in tissue culture (Brawn 1970, Hellstrom & Hellstrom 1975). Recent work in collaboration with Professor L. Brent and Dr I. Hutchinson has also revealed anti-embryo antibodies in mice that have received injections of irradiated embryonic cells. Such antibodies are also found in the sera of multiparous rats (Rees, Price & Baldwin 1979).

Anti-embryo immunity is aroused by the deliberate inoculation into mice of embryonic tissue of a suitable age; and for reasons still unknown the embryo tissue must first be irradiated; alternatively, as already mentioned, immunity may arise as a concomitant of one or more syngeneic pregnancies, a phenomenon which suggests that the need to irradiate embryonic tissues before they are injected into adults to arouse immunity has probably some quite trivial explanation. The central argument of this paper grows out of putting considerations A and B together, i.e. out of putting together anaplasia and anti-embryo immunity; for if anaplasia occurs, i.e. if there is a partial retrogression towards embryonic characteristics in tumour cells, and if the embryo substances formed anew should happen to include those that give rise to transplantation immunity, then the inoculation into mice of embryo tissue should confer protection against the growth of tumours. It may even be that this is why so many tumours do arouse a feeble immunity of the cellular type.

There is indeed abundant evidence that the inoculation into adult animals of irradiated embryonic tissues may bring about a change of state that delays the onset and diminishes the final total frequency of tumours aroused by experimental means; evidence that this is indeed the case has been summarized by Coggin & Anderson (1974) and Anderson & Coggin (1971) who were among the prime movers in this research, by Alexander (1972) and by Rees, Price & Baldwin (1979) and Castro, Hunt, Lance & Medawar (1974). The experimental tumours that enjoy the protection produced by inoculation beforehand of irradiated embryonic tissues include tumours aroused both by oncogenic viruses and by oncogenic chemicals.
Protection Against Chemically-induced Tumours in Mice by Inoculation of Embryonic Tissue

The experiments now to be described illustrate a number of properties of tumour immunity that are very relevant to the interpretation of MacMahon’s epidemiological findings as illustrated in Figure 2.

Except where otherwise stated all the experiments were done with highly inbred mice of strain CBA using as a cancer-provoking agent a subcutaneous injection of 50μg of 3-methylcholanthrene (MCA) in olive oil. The fetal inoculum consisted of a coarse triturate. Before injection the embryonic cells were exposed to 2000r gamma irradiation from a cobalt-90 source. The relative timing of MCA and embryonic tissue injections turned out to be the most important independent variable in our experiments. We have adopted the convention that the day of injection of MCA is always entered as Day 0, and the experiments were continued a year after the injection of carcinogen.

In our first experiment (Figure 3), in which an attempt was made to use embryonic tissue therapeutically, a large group of male CBA mice each received injections of 50μg MCA on Day 0; of these half were given no other treatment and the other half half received an injection of fetal tissue at 90 days—just before the time at which the first tumours were expected to appear. The graph makes it clear that there was no therapeutic effect: if anything, the injection of fetal tissue made matters worse—had caused tumours to appear more rapidly and more often.

The experiment illustrated by Figure 4 was of exactly the same design except that on this occasion fetal tissue was injected 14 days before the administration of MCA; that is to say, the fetal tissue was injected on Day −14 according to our convention. Here a protective effect was clearly apparent. Tumours in the mice that received fetal tissue before MCA arose more slowly and less often.

![Graph showing per cent incidence of tumours arising in control versus syngeneically sensitized mice (CBA♂)](image)

Figure 3. Illustrating how the inoculation of fetal tissue after exposure to an oncogenic stimulus may enhance the growth of tumours: in this experiment two sets of 25 male CBA mice received an inoculum of methylcholanthrene on Day 0; of these one-half received 1×10⁶ irradiated 14-day-old PBA mouse embryo cells 90 days later (see text).
Figure 4. An experiment of exactly the same design as that which is illustrated in Figure 3 except that on this occasion inoculum of fetal tissue was administered 14 days before the cancer-provoking injection of methylcholanthrene. On this occasion the fetal tissue has conferred a highly significant degree of protection.

On the basis of these two experiments we formed the hypothesis that tumour resistance of the type aroused by the injection of fetal tissue was of the kind known in transplantation immunity as highly 'enhanceable'. We surmised that a malignant transformation took place fairly soon after the inoculation of MCA and that the inoculation of fetal tissue would have to be done before this event occurred; if it were to be postponed, matters would be made worse. The experiment illustrated by Figure 5 bore out this expectation. Five groups of 25 CBA mice received an inoculation of

Effect of fetal tissue given at various intervals before or after injection of MCA (50 μg)
MCA day 0, FT as shown

Figure 5. An experiment in which five sets of 25 male CBA mice received inocula of irradiated fetal tissue at various times before or after the administration of methylcholanthrene: inoculation of fetal tissue before MCA exerted a much more highly protective effect than an inoculation at the same time (Day 0) or 7 or 14 days afterwards. The experiment is fully described in the text.
MCA (Day 0). The five groups of mice received their fetal inocula either on the same occasion (Day 0) or 7 or 14 days before (−7, −14) or 7 or 14 days later (+7, +14).

The results (Figure 5) were admirably clear – the tumours arose more slowly and less often in the groups of mice that had received fetal tissue 7 or 14 days before MCA than in mice of all other groups, and injection at Day +14 led to the formation of more tumours than injection at Day 0 or Day +7.

These experiments showed – as many others have since confirmed – that in the protection of mice against tumours by quasi-immunological means we are balancing on a knife edge between prophylaxis and enhancement. This may be why clinical experience with tumour immunotherapy has so far given such inconclusive and in the main disappointing results, for in the clinical situation relative timing of the malignant change and any attempted therapeutic inoculation will almost inevitably be such as to favour the enhancement of tumour growth, so making matters worse. These arguments need not apply, of course, to the non-specific immunopotentiating of resistance such as that which is thought to be brought about by the administration of BCG or Corynebacterium parvum.

Relevance to Human Breast Cancer

The experiments reported upon so far have no very obvious bearing on the incidence in human beings of breast cancer and its relationship to age at birth of first child (Figure 2).

The connecting link is that the change of state produced by the inoculation of fetal tissue is produced also by pregnancy: the spleens of mice which have borne a number of litters have been found to contain cells cytotoxic to embryonic cells and to some tumour cells in vitro (Brawn 1970, Hellstrom & Hellstrom 1975); moreover the sera of multiparous rats contain antibodies reacting upon rat embryo cells (Rees, Price & Baldwin 1979).

R. C. Moon (1969) and more recently Pinto and Greveson working at the Clinical Research Centre, Harrow, have shown that the bearing by rats of a single litter affects their susceptibility to the tumours formed by the oral administration of dimethylbenzanthracene (DMBA) and have kindly allowed us to reproduce results of an early experiment in Table 1. This experiment made use of three groups of rats of a closed colony belonging to the Sprague Dawley strain. All rats received 20 mg DMBA in 1 ml olive oil by mouth. One group of rats received no other treatment and rats of the other two groups were caused to go through one complete pregnancy either before

<table>
<thead>
<tr>
<th></th>
<th>No. with tumours</th>
<th>No. without tumours</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous controls</td>
<td>19</td>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>Litter after DMBA</td>
<td>10</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Litter before DMBA</td>
<td>1</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>
or after the administration of DMBA. It can be seen by inspection of Table 1 that pregnancy after the administration of carcinogen had no significant influence on tumour incidence, though a pregnancy before the administration of carcinogen exercised a clearly significant protective effect.

Although the relevance of such findings to human beings may naturally be questioned, it is fair to ask what prediction would be made about the risk of breast cancer in human beings if it were indeed possible to translate our experimental findings directly into clinical terms.

Our prediction would necessarily be that passage through a pregnancy before any malignant transformation occurred would exercise a protective effect, whereas a pregnancy after any precancerous transformation happened, so far from exercising any protective effect would make matters worse, i.e. would give rise to the phenomenon of ‘enhancement’. Reference to MacMahon’s epidemiological study, summarized in Figure 2, shows that such predictions are exactly borne out: the clinical findings are compatible with our hypothesis, which is not of course to say that they ‘prove’ it.

Is a Cancer Vaccine Possible in Principle?

If anaplastic reversion – i.e. a reawakening of what would otherwise have been silent fetal genes – regularly accompanied the malignant transformation, and if – as appears to have been the case in our own experiments – the derepressed fetal genes programme for substances that confer heightened resistance against tumours, then the search for a protective vaccine would represent a realistic ambition; indeed, if our interpretation of MacMahon’s epidemiological findings is correct a teenage pregnancy itself represents a kind of vaccination against tumours arising later in life. Disregarding the question of whether a state of heightened resistance to induced tumours can properly be described as an ‘immunity’ in the technical sense, it is clear that if our interpretation is correct the search for a cancer vaccine is in effect the search for some means to call into being the state of heightened resistance produced by an early first pregnancy.

Unfortunately, the nature of the ‘antigens’ that bring about the change of state that discourages the growth of tumours is not yet known – it is not even known if the fetal substances known empirically to be effective can be so described.

![Figure 6. Illustrating the development of tumours in five sets of 25 male CBA mice which received inocula of a variety of irradiated adult tissues 14 days before the administration of methylcholanthrene. The thymus exercised a clearly protective effect, but the other adult tissues were ineffective.](image-url)
Whatever uncertainties there may be about the change of state produced by the inoculation of fetal tissues, it is quite certain that the use of human fetal tissues for such a purpose is out of the question. Everything therefore turns upon the discovery of some effective alternative source of protective 'antigens'—perhaps in the form of some easily available quasi-embryonic tissue that can be secured from adults.

One such tissue is testicular tissue—in effect a mixture of spermatagonia, spermatocytes, spermatids and spermatozoa. Some years ago Medawar & Hunt (1976) gave evidence that irradiated testicular cells, administered as if they were embryonic cells, protected mice against MCA-induced tumours to about the same degree as do embryonic tissues. The evidence originally cited was not very extensive, but many experiments carried out since have confirmed us in our supposition that testicular cells exercise a protective effect. It is also very relevant that, like embryonic tissue, testicular tissue can also produce 'enhancement' when injected after the cancer-producing dose of MCA.

This is not the only possibility currently under investigation. Medawar & Hunt (1978) reported that an inoculation into mice of a miscellany of adult tissues enhanced the growth of MCA tumours much as inocula of fetal tissues enhanced the growth of such tumours when the adult tissues were injected after MCA (see Figures 3 and 5). Believing as we do that enhancement and protection are simply opposite sides of the same coin we accordingly screened a number of adult tissues under conditions that should have made it possible for them to exercise any protective power that they may have possessed. The results of this experiment are shown in Figure 6 which illustrates the outcome of inoculating into mice dissociated and irradiated adult cells from various sources 14 days before the administration of 50μg MCA. In the outcome irradiated thymic tissue exercised a clearly significant ($P<0.02$) protective effect. Our current research is concentrated upon finding out if the evidence for this protective effect can be confirmed and strengthened. The most recent results have been confirmatory.

**Discussion**

Doubts have often been expressed—by ourselves among others—about the propriety of describing as 'immunity' the change of state brought about by the inoculation of embryonic or quasi-embryonic tissues into adult mice. In the early days of transplantation exactly comparable doubts were expressed about whether what is now called 'transplantation immunity' deserved to be so described; these doubts were eventually set at rest by recognition of the existence of cell-mediated immunity and by the demonstration of specific humoral antibodies by P. A. Gorer (see the review by Medawar 1961).

Of course, from a pragmatic point of view the name of the phenomenon does not matter: the importance of the hypothesis of immunity lies principally in guiding future observations and experiments, especially in the search for antibodies and for evidence of specificity generally. It must be said, however, that any possible use of prophylactic measures based upon the principles we have been discussing could be compromised by the knife-edge balance to which we have called attention between discouraging tumour growth and enhancing it. Another important consideration is that no clinical trial of a supposedly efficacious prophylactic procedure could be judged thorough unless it lasted for 50–60 years, this being approximately the duration of the protective effect of early pregnancy that has been revealed by the epidemiological research of MacMahon.
References