against cellular—including tumour—antigens, and probably many cases of supposed tolerance are due to blocking or enhancing antibodies.

Leukaemogenic Viruses

The second group of naturally occurring oncogenic viruses in mice is the leukaemogenic viruses. Most mouse strains carry leukaemogenic viruses related to Gross virus, which are transmitted vertically from mothers (and sometimes from fathers) to offspring. For many years it was thought that animals were tolerant to such viruses, producing neither antibody nor cell-mediated immunity. If that were the case, immunosuppression would not be expected to affect tumour development. In fact, it does. Thymectomy cannot be used in this situation, because the production of leukaemia by both the Gross and the Moloney virus requires the presence of a thymus. However, Allison and Law⁷ found that Moloney lymphoma or leukaemia was greatly potentiated by inoculations of antilymphocytic serum. We have found that the latent period for leukaemia induction in AKR mice, which carry the Gross virus, is shortened by the administration of antilymphocytic serum.

Wahren and Metcalfe¹² have found that lymphocytes from AKR mice are cytotoxic to target cells carrying the Gross virus, so that they can no longer be regarded as tolerant. Other evidence that this is so has been presented by Dore *et al.*¹³ In this case nearly all animals left long enough develop leukaemia (after a latent period of about 300 days). Immunity does not prevent leukaemia but delays its onset, which allows the animals to breed before onset of malignancy. Immunosuppression accelerates the malignancy.

Immunological Surveillance

All these results leave little doubt that the immunological surveillance mechanism operates very efficiently against virus-induced tumours in animals, either preventing or delaying the onset of malignancy. All the tumours so far found in mice receiving long-term immunosuppression have been leukaemias, lymphomas, or mammary tumours, or polyoma-induced tumours of the salivary glands or osteosarcomas. In all these cases there is reason to believe that a virus may be concerned in the aetiology. Though the surveillance mechanism may also operate against tumours not induced by viruses, there is no direct evidence that this is the case. Nevertheless, it would be premature to conclude that the tumours occurring in human patients treated with immunosuppressants are virus-induced, though the parallel between animals is striking enough to demand further analysis.

REFERENCES

- ¹ Huebener, R. J., *Harvey Lectures*, 1961, 56, 45.
- ² Dulbecco, R., *Science*, 1969, 166, 962.
- ³ Law, L. W., *Cancer Research*, 1966, 26, 551.
- ⁴ Allison, A. C., and Taylor, R. B., *Cancer Research*, 1967, 27, 703.
- ⁵ Gaugas, J. M., *et al.*, *Nature*, 1969, 221, 1033.
- ⁶ Ptak, W., Gaugas, J. M., Rees, R. J. W., and Allison, A. C., *Clinical and Experimental Immunology*, 1970, 6, 117.
- ⁷ Allison, A. C., and Law, L. W., *Proceedings of the Society for Experimental Biology and Medicine*, 1968, 127, 207.
- ⁸ Allison, A. C., in *Proceedings of the Fourth Quadrennial Cancer Conference*, Perugia, p. 376, 1970.
- ⁹ Billingham, R. E., Brent, L., and Medawar, P. B., *Nature*, 1953, 172, 603.
- ¹⁰ Billingham, R. E., and Brent, L., *Proceedings of the Royal Society (Series B)*, 1956, 146, 78.
- ¹¹ Hellström, I., Allison, A. C., and Hellström, K. E., *Nature*. In press.
- ¹² Wahren, B., and Metcalfe, D., in *Proceedings of the Fourth Quadrennial Cancer Conference*, Perugia, p. 473, 1970.
- ¹³ Doré, J. F., Ajouria, E., and Mathé, G., *Revue Européenne d'Études Cliniques et Biologiques*, 1970, 15, 8.

Immunosurveillance and Cancer: Epidemiological Evidence

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The mechanism by which cancer develops remains one of the great mysteries of modern medicine. The concept that it results from a breakdown in "immunological surveillance," which permits the proliferation of an abnormal clone of cells with a selective advantage over other cells, has been widely welcomed as a stimulus to thought and experiment. Keast¹ has recently summarized the evidence for this hypothesis under four heads. Firstly, cancer in man occurs characteristically at the extremes of life when the immune system is either maturing or is weakened by thymic atrophy. Secondly, its incidence is increased following the use of immunosuppressive drugs. Thirdly, the same effect is produced experimentally by thymectomy in mice. Fourthly, the rare diseases that involve a deficiency of cell-mediated immunity are characterized by a high incidence of tumours in those subjects who survive long enough to allow their development.

In the present paper we review only those parts of the evidence that have been obtained from observations on man.

Immunological Disorders

Consider first the frequency with which cancer has been reported in association with immunological disorders. These include three congenital disorders—ataxia-telangiectasia and the Wiskott-Aldrich and Chediak-Higashi syndromes.

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The first is an autosomal recessive trait characterized by progressive cerebellar ataxia in childhood, telangiectases (particularly in the conjunctiva), and an increased susceptibility to respiratory infections. Malignant tumours have been recorded in no fewer than 14 out of the 200 cases reported, including five reticulum cell sarcomas, two cases of Hodgkin's disease, two lymphosarcomas, and two gastric carcinomas. The immunological defect has not been specified, but it involves defective cellular immunity and antibody response to antigen and shows abnormalities in the level of serum immunoglobulin and in the thymus.²

The Wiskott-Aldrich syndrome affects boys, producing thrombocytopenia, eczema, and recurrent infections. Most die early from haemorrhage or infection, but despite this malignant tumours, mainly reticuloendothelioses, were present in 11 of the 90 reported cases. Immunoglobulin levels, cellular immunity, and antibody response to antigen are initially normal, but subsequently the serum immunoglobulin decreases and small lymphocytes disappear from the circulation and the lymph nodes.³

The Chediak-Higashi syndrome is an autosomal recessive trait, characterized by distinctive granule-containing leucocytes, a pigment defect in the skin, hair, and eyes, and again a pronounced susceptibility to infection. In at least 11 out of the 50 reported cases a terminal illness has developed in which the appearance of the lymphoid tissue suggested a lymphoma. The nature of the immunological deficiency has not yet been discovered.⁴

A fourth congenital disorder, agammaglobulinaemia, is better considered together with hypogammaglobulinaemia. These conditions, when not due to some other disease, present a wide variety of clinical and pathological features. Cases with onset in infancy tend to be in males with a positive family history, but this is not an absolute rule and the classification of individual cases may be extremely difficult. Many cases that appear to be acquired may

have a genetic basis and we have preferred to follow the lead of the Medical Research Council's Working Party⁵ on the treatment of hypogammaglobulinaemia by classing all the supposedly primary cases together.

An association with malignancy was first recorded in 1963 of the development of acute lymphatic leukaemia in a boy of 4 with a reasonably secure diagnosis of congenital agammaglobulinaemia.⁶ In some other cases it is difficult to exclude the possibility that the serum protein deficiency may have been an early manifestation of the malignancy. Thus of 14 malignant tumours among patients registered in the Medical Research Council's study, seven were diagnosed within two years of the discovery of the serum deficiency; some of these, however, had a previous history of recurrent infections over many years. Four of the remainder (a case of Hodgkin's disease, a reticulosarcoma, a gastric carcinoma, and a carcinoma of the cervix uteri) were diagnosed more than five years after the serum protein abnormality was discovered.

Several other less obviously immunological disorders have been thought to be associated with an increased incidence of reticuloses. But the evidence is convincing only for Sjögren's syndrome. Among 58 affected patients Talal and Bunim⁷ found three cases of reticulum cell sarcoma, while a further four cases of this association have been reported. The high incidence of lymphomas, and perhaps also of carcinomas, in gluten-enteropathy⁸ and of colonic cancers in ulcerative colitis could also be related to immunological reactions—if, as some people suppose, these disorders are autoimmune in origin.

Thymectomy

What part the thymus normally plays in immune reactions remains in doubt. Absence of the thymus is associated with gross defects of the immunological system, but children with this defect have not survived long enough to show what effect this might have in adult life. In adults only two groups of patients have been subjected to thymectomy in any large number—that is, patients suffering from a thymoma or from myasthenia gravis. The number of patients are few, but the little evidence that there is provides no reason to suppose that either the operation or the presence of myasthenia gravis is associated with an increased incidence of any other disease. Vessey⁹ has collected observations on 419 patients who had a thymectomy at one of four London hospitals between 1942 and 1964. Of the 314 available for review, five had died of cancer and eight others are known to have developed the disease (three after the end of the follow-up period). Comparison between the number of deaths observed and the number that would have been expected at national mortality rates provides no evidence of any increased mortality. The thirteen cancers include three carcinomas of the breast, two carcinomas of the skin, and one each of gastric carcinoma, bronchial carcinoid, pituitary adenoma, osteogenic sarcoma, astrocytoma, Hodgkin's disease, chronic lymphatic leukaemia, and carcinomatosis of unknown origin. The average duration of complete follow-up was only 12.3 years and it is too soon to draw any firm conclusions. But, so far as they go, the data provide no evidence that thymectomy in adult life leads to any special risk either of cancer as a whole or of any particular type.

Therapeutic Immunosuppression

Much the most important evidence comes from the occurrence of malignant tumours following immunosuppression for organ transplants between non-identical twins. Within a few years of the introduction of renal transplantation, the inadvertent transplantation of cancer was reported.⁹⁻¹² At that time, kidneys were transplanted from patients dying with malignant disease, so long as they were free from metastases on macroscopic examination. In all seven cases have been recorded in which the tumour had spread from the donor's primary in the breast (2 cases), bronchus (2 cases), thyroid, liver, or larynx,

and there has been one case in which the transplanted kidney contained a primary hypernephroma.

The behaviour of the neoplasm in the recipients has sometimes been most unusual. In one case¹³ the primary tumour was in the donor's bronchus and presented in the recipient as an abdominal mass. Surgery failed to remove the tumour entirely, but the cessation of immunosuppression was followed by the complete disappearance of neoplastic tissue at a subsequent laparotomy. In another case¹⁴ withdrawal of immunosuppression was followed by disappearance of pulmonary metastases. Such observations strongly suggest that the immunosuppression facilitated the growth of the malignant tissue.

Over 40 primary malignant neoplasms—including carcinoma-in-situ—have now been recorded in the recipients of organ transplants while on immunosuppressive treatment.¹⁵ The finding of carcinomas-in-situ in the cervix uteri is not perhaps of much significance and neither may be the nine cancers of the skin or lip, but the frequency of mesenchymal tumours is impressive (see Table). Possibly about 4,000 renal transplants have been performed to date,¹⁵ and the occurrence

Malignant Neoplasms Developing De Novo in Transplant Patients on Immunosuppressive Therapy¹⁵

Neoplastic Disease	No. of Cases
Reticulum cell sarcoma ..	12
Other lymphomas ..	3
Gastrointestinal carcinoma ..	2
Skin and lip carcinoma ..	9
Carcinomatosis ..	2
Other carcinomas ..	4
Inadequate information ..	5
All neoplasms ..	37
Carcinoma-in-situ (cervix uteri) ..	5

of 12 reticulum cell sarcomas and two other lymphomas in this number of patients contrasts strongly with the infrequent occurrence of reticuloses in the general population (an annual rate of 20 cases of reticuloses other than Hodgkin's disease per million population at ages 20-49 years¹⁶). If the transplant patients were kept under observation for an average of four years, the reported cases would imply an increase in the incidence of reticulosis of at least 50-fold.

The immunosuppressive drugs administered were in all cases azathioprine and prednisone; antilymphocytic globulin was also administered in eight cases; splenectomy was performed in 18 cases and thymectomy in five. In one case a reticulum cell sarcoma developed at the site of the antilymphocytic globulin injections and in four cases a similar tumour was detected only in the brain, which is not a common site of involvement by reticulosarcomas. Several of the lymphomas developed within a year of the transplant.

Transplant patients will need to be followed up for much longer before we can tell with certainty whether cancers other than lymphomas occur with increased frequency. The use of immunosuppressive drugs in the treatment of non-malignant conditions like rheumatoid arthritis, ulcerative colitis, and the nephrotic syndrome will help in separating the contribution of immunosuppression from the contribution of the foreign lymphoid elements, with their associated antigenic stimulation. With the help of the Cancer Research Campaign, a long-term study has recently been set up to investigate this problem and surgeons and physicians are co-operating by reporting all patients who are under their treatment to a centre in Oxford. One report of lymphosarcoma developing in a patient with proliferative glomerulonephritis shortly after a year's course of immunosuppressive therapy has already been received.

Age Distribution of Cancer

The age distribution of cancer is sometimes cited as evidence of an association with defective immunological control. Certainly, the two common patterns are (1) a peak incidence in infancy or childhood, and (2) a rapid, uninterrupted, and fairly regular increase in incidence from adolescence to old age. There is, however, a wide variety of patterns between

these extremes. Cancers like seminoma of the testis and some varieties of Hodgkin's disease show a peak incidence in young adult life. Others like carcinoma of the corpus uteri decrease in incidence in old age, while the incidence of carcinoma of the cervix uteri remains practically constant after about 45 years of age. Explanations can be found for most of these patterns, but the fact remains that there are as many exceptions to the two "typical" patterns as there are examples.

Examination of the pattern of age-specific incidence rates of those cancers that increase in incidence with age shows that the incidence increases approximately in proportion to a power of the age, commonly the fourth, fifth, or sixth power. This pattern is not limited to cancer and is shown by other degenerative diseases, which, it may be argued, provides evidence that they are all related to some nonspecific process of ageing. More detailed examination suggests, however, that the increase in incidence may depend not so much on age as such as on the duration of exposure to a carcinogenic agent, and that the most characteristic pattern is one in which incidence is proportional to about the fourth power of the duration of exposure. This pattern, for example, is shown both by bronchial carcinoma in cigarette smokers and by skin cancer in mice which have been painted at regular intervals with one or other of several carcinogenic agents.⁹

Age at Exposure

Most sources of data available show that the incidence of cancer increases with age at exposure. The clearest evidence derives from patients who have been irradiated for ankylosing spondylitis, among whom the incidence of leukaemia attributable to irradiation increased from approximately 2.7 per 1,000 in patients irradiated at ages 15 to 24 years to 10.6 per 1,000 among patients irradiated at ages 60-69 years.^{17,18} Other evidence derives from a group of men who were employed in a nickel refinery in South Wales before 1925, 40 of whom (8%) developed cancer of the nasal sinuses. After allowance was made for date and duration of exposure the incidence was found to increase four-fold between men whose ages at first employment were respectively under 20 years of age and 35 years or more.¹⁹ Three other industries have also provided similar observations relating to the incidence of tar-warts in men who made gas from coal,^{20,21} cancer of the lung in asbestos workers,²² and cancer of the bladder in chemical workers exposed to β -naphthylamine, α -naphthylamine, or benzidine.²³

Two sets of data, however, provide results which point in a different direction. Firstly, Bizzozero *et al.*²⁴ found that the incidence of leukaemia among the Japanese who survived exposure to the atomic bomb explosions at Hiroshima and Nagasaki and who were within 1,500 metres of the hypocentre of the explosion, was unrelated to age, except for a somewhat higher incidence in those who were less than 10 years old at the time of exposure. Secondly, the incidence of occupational cancers of the lung in nickel workers increased with age at first employment only up to 25 years of age and then fell.¹⁹

These studies are all based on substantial numbers and the difference between the results cannot be attributed to chance;

nor can it be attributed to a difference in the extent to which men and women of different ages were exposed to the carcinogenic agent. Indeed, the conflicting observations for cancers of the lung and nasal sinuses were made on the same group of men. One possible explanation is that the effect of age on the susceptibility to cancer induction is not always the same but varies with the extent to which the tissue has already been exposed to other agents.¹⁷ Be that as it may, we cannot use the present data to support the hypothesis that the appearance of cancer is determined to any important extent by an ageing process that is independent of the amount and duration of exposure to carcinogenic agents.

Conclusion

We must conclude that the four sources from which Keast¹ sought evidence provide only very weak support for the idea that the appearance of clinical cancer is generally the result of a breakdown in immunological surveillance. That is not to say that the idea is wrong, nor that immune mechanism cannot be utilized effectively for treatment of established disease. The evidence that we have reviewed points to a close association between immunological disorders and the development of cancers of the reticuloendothelial system, but this does not necessarily imply cause and effect. Both may be due to a common cause. A key question is whether intensive immunosuppression will lead to an increased frequency of other types of cancer and whether this is so or not remains to be seen.

REFERENCES

- ¹Keast, D., *Lancet*, 1970, 2, 710.
- ²Dent, P. B., Peterson, R. D. A., and Good, R. A., *Birth Defects. Original Articles Series*, 1968, 4, 378.
- ³Cooper, M. D., Chase, H. P., Lowman, J. T., Krivit, W., and Good, R. A., *Birth Defects. Original Articles Series*, 1968, 4, 443.
- ⁴Windhurst, D. B., White, J. G., Dent, P. B., Decca, J., and Good, R. A., *Birth Defects. Original Articles Series*, 1968, 4, 424.
- ⁵Medical Research Council Working Party, *Lancet*, 1969, 1, 163.
- ⁶Page, A. R., Hansen, A. E., and Good, R. A., *Blood*, 1963, 21, 197.
- ⁷Talal, N., and Bunim, J. J., *American Journal of Medicine*, 1964, 36, 529.
- ⁸Vessey, M. P. Personal Communication.
- ⁹Maclean, L. D., *et al.*, *Archives of Surgery*, 1965, 91, 288.
- ¹⁰Dossetor, J. B., Presented at Washington Conference on Human Kidney Transplants, May 1965.
- ¹¹Martin, D. C., Rubin, M., and Rosen, V. J., *Journal of the American Medical Association*, 1965, 192, 752.
- ¹²McPhaul, J. J., and McIntosh, D. A., *New England Journal of Medicine*, 1965, 272, 105.
- ¹³Wilson, R. E., *et al.*, *New England Journal of Medicine*, 1968, 278, 479.
- ¹⁴Zukoski, C. F., *et al.*, *Transplantation*, 1970, 9, 71.
- ¹⁵Penn, I., Third International Congress of the Transplantation Society and Personal Communication, September 1970.
- ¹⁶Waterhouse, J. A. H., Lev, J. M., and Powell, J., in *Cancer Incidence in Five Continents*, ed. R. Doll, M. S. Muir, and J. A. H. Waterhouse, vol. 2, Geneva, U.I.C.C., 1970.
- ¹⁷Doll, R., *Dorn Memorial Lecture*, 10th International Conference of the International Union against Cancer, Houston, U.S.A., May 1970.
- ¹⁸Doll, R., and Kinlen, L., 1970. To be published.
- ¹⁹Doll, R., and Morgan, L., and Speizer, F., *British Journal of Cancer*, 1970. In press.
- ²⁰Fisher, R. E. W., In *Proceedings of the 12th International Congress on Occupational Health*, vol. 3, p. 402. Helsinki, Valtioneuston Kirjapaino, 1958.
- ²¹Doll, R., *Acta: Unio Internationalis Contra Cancrum*, 1964, 20, 747.
- ²²Knox, J. F., Holmes, S., Doll, R., and Hill, I. D., *British Journal of Industrial Medicine*, 1968, 25, 293.
- ²³Case, R. A. M., Hosker, M. E., McDonald, D. B., and Pearson, J. T., *British Journal of Industrial Medicine*, 1954, 11, 75.