ISSN 0025-7680

TUMOR IMMUNOLOGY REVISITED
International Symposium
Academia Nacional de Medicina
Buenos Aires, 27 August 1996

MEDICINA (Buenos Aires) 1996; 56 (Supl I): 74-82

IMMUNE MECHANISMS AND TUMOR DORMANCY*

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Summary The natural occurrence of tumor dormancy in man is reviewed based on observations made by a distinguished surgeon and two pathologists after a lifetime of practice.They concluded that dormancy is the result of immune mechanisms preventing the growth of microscopic metastases already present following curative surgery. Six cases of non-small-cell lung cancer are described in patients randomized to receive specific active immunotherapy in controlled clinical trials. Three patients had nonregional metastases at 11, 12 and 14 years. Two had regional recurrence after 9 years and in one patient a small hilar-node metastasis was found at necropsy after 7.6 years. In each case an immunodepressive event or drug treatment preceded resurgent growth. Animal models of tumor dormancy are reviewed and the evidence is clear that dormancy may be induced by manipulating immune mechanisms, resulting in cells remaining in mitotic arrest, or tumor cell proliferation is balanced by an equivalent rate of cell death. Based on these observations future clinical strategies should be developed to induce the dormant state in micrometastases in the adjuvant setting.

The phenomenon of tumor dormancy in man has long been recognized. It is worthwhile quoting the opinions of distinguished surgeons and pathologists which show remarkable insights, gained after a lifetime of observation, that in more recent years have been shown to be accurate in terms of inducing, maintaining and terminating the dormant state. In 1959, Gordon-Taylor described some 50 years of his personal observations[1] as a surgeon in London. «Those unknown forces which can keep cancer cells dormant in the vicinity of the excected primary tumor or in the lymph nodes of distal anatomical regions for a mammoth number of years before their resurgence point to a great auxiliary defensive power resident in the host in some cases. Dormant cancer cells are prone to lurk in or near the site of the original operation, in regional lymph nodes or in deeply placed organs. Such foci must have been implanted before or during the excision of the primary neoplasm». His comments on causal factors in recurrence are worth noting. «In some cases no causal factor, save possibly advancing age can be impugned as standing in any relationship to the recurrence of the malady, but in others recurrence does appear to have been preceded by intercurrent disease or by surgical operation for some independent condition. In those cases cancer resistance or cancer immunity, long maintained, appears to have been broken down by happenings unconnected with the original malady».

Geoffrey Hadfield was a senior pathologist who worked in London before and during the second world war. He became Dean of the Institute of Basic Medical Sciences and in 1954 he gave a memorial lecture[2]. The following is taken from his paper entitled The Dormant Cancer Cell. «It seems impossible to escape the conclusion that the cells of the dormant growth are in a state of

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* Lecture delivered at the Instituto de Oncología Angel H. Roffo, en memory of Dra. Rosa Rabinovich de Pirosky.

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temporary mitotic arrest. For the sake of brevity in choosing a title for this lecture I have used the word «dormant» to describe malignant cells which, although remaining alive in the tissues for relatively long periods, show no evidence of multiplication during this time, yet retain all their former and vigorous capacity to multiply».

The Australian pathologist Rupert Willis, famous for his text The Spread of Tumors in the Human Body, first published in 1934, had a section in the Third Edition[3] in 1973 entitled "Delayed growth of metastatic tumors". He concluded; «Long delay in the germination of disseminated tumor cells and arrest of growth in already established metastases must denote the operation of potent bodily forces antagonistic to the growth of the particular tumors».

These opinions, stated 20 to 40 years ago, are in close agreement as to the initiation, maintenance and termination of tumor dormancy in humans (Table 1). In Table 2 are listed a group of human tumors in which dormancy has been observed tabla 1; notable by its absence in lung cancer.

In this context, we describe therefore six cases of *non-small-cell lung cancer* that were treated in Ottawa. These patients exhibited moderate to very strong delayed hypersensitivity reactions to soluble lung cancer membrane antigen after specific immunotherapy. Three patients had nonregional metastases at 11, 12 and 14 years with no new primary tumor found. Two had regional recurrence after 9 years, and in the last patient a small hilar node metastasis was found at necropsy 7.6 years following lung surgery. *In each case an immunodepressive event or drug treatment preceded resurgent growth.*

TABLE 1.— *Conclusion of distinguished pathologists and surgeons on mechanisms of tumor dormancy*

Introduction	Metastases at time of surgical excision are prevented from growing by a potent force causing mitotic arrest
Maintenance	This host resistance, long-maintained cancer immunity, is susceptible to breakdown
Termination	Advancing age, distress of surgery, herpes zoster, endogenous depression

TABLE 2.— *Tumors in which dormancy has been observed (after Gordon-Taylor)*

Carcinoma of breast	Carcinoma of body of pancreas
Carcinoma of stomach	Carcinoma of kidney
Carcinoma of colon	Osteoblastic sarcoma
Carcinoma of rectum	Intraocular melanoma
Wilms' tumour	Carcinoma of tongue, cheek, lip
Melanoma	Carcinoma of hypopharynx and esophagus

In 1977 we published[4] a survival study on a group of 55 patients with stage I or stage II (American Joint Committee for Cancer Staging and End Results Reporting) carcinoma of the lung who were in a randomized trial of specific active immunotherapy. (Details of the preparation of soluble allogeneic and autologous antigens have been described[5], also the use of Freund's complete adjuvant and high-dose methotrexate with citrovorom rescue given because it causes a vigorous rebound in immune reactivity 9 days after injection). In particular we reported on the strengths of delayed hypersensitivity reactions (DHR) seen on late testing of various subsets of patients with soluble cancer antigen derived from autologous or allogeneic sources (Fig. 1). The strongest reactions, mean greatest diameter at 48 hours, were seen in the 13 patients who had received immunochemotherapy, followed by the 16 patients who had received immunotherapy, and both groups had stronger reactions than the 26 nonimmunized patients. We suggested in 1977 that these strong reactions reflected a heightened cellular defence against microscopic foci of residual disease. In 1982 both groups of immunized patients showed significantly better survival than nonimmunized patients[6]. Eight of the 13 patients with the strongest DHR survived more than 10 years and 3 had nonregional metastases discovered 11, 12, and 14 years after the primary surgery. The case histories of two of these patients have been described in detail[7].

Case 1. The first, a 58-year-old man, had a 9 cm poorly differentiated adenocarcinoma, T2NO, removed by a left pneumonectomy in October 1976. He received immunochemotherapy and in 5 months he was skin

tested with 100 µg of antigen. An 11 x 10 mm of reaction was noted at 48 hours. Eleven years later he had a 20 x 7 mm reaction to 100 µg of adenocarcinoma antigen. In July 1987 a cerebral metastasis was discovered (adenocar-cinoma) and an intense search failed to reveal a new primary tumor. A liver computed tomography scan showed no evidence of tumor at the time of staging of the metastatic tumor. Five months after cerebral irradiation and systemic administration of steroids a liver metastasis was found which grew until his death 13 years after primary surgery.

Case 2. The second was a 40-year-old man who had a left pneumonectomy in March 1974 for adenoid cystic carcinoma 4 cm T2NO, arising from an upper lobe bronchus. Fifteen months after surgery and immunochemotherapy he had developed a moderate DHR to tumor antigen, 15 x 15 mm which strengthened to 31 x 31 mm at 10 years. Six years after surgery he had an acute myocardial infarction. At the 12th year following surgery, in 1986, he presented with painful liver metastases. The liver metastases had the same characteristic histology as the primary tumor. At necropsy 6 weeks later his right lung was free of tumor.

Case 3. In August, 1973 this 57-year-old woman presented with two primary adeno-carcinomas of the right upper lobe, one poorly differentiated, one well differentiated, 4.5 cm and 2.5 cm respectively, T2NO. A parietal pleura resection at the apex was needed because of adhesions. Two years post vaccination she had developed a very strong DHR to adenocarcinoma antigen (56.5 µg) - 55 x 35 mm. In 1980 she developed an endogenous depression severe enough to warrant admission to hospital. She attended a psychiatric outpatient clinic for the next seven years, with a further hospital admission in October 1985. In 1983, when depressed, she was again skin tested with 100 µg of adenocarcinoma antigen and showed a reduced reaction, 20 x 19 mm. In September 1987 she was asymptomatic but a 2 cm right-sided supraclavicular node was removed just adjacent to the remote parietal pleura resection containing adenocarcinoma. An intense search did not reveal a new primary tumor. In November, 1987 a 1.5 cm lesion was found in the left upper lobe, growing to 2.0 cm in March, 1988 when it was removed, an adenocarcinoma. In April, 1989 the patient was cheerful, had gained 4.0 kg in weight, and on retesting with 100 µg of adenocarcinoma antigen again showed a very strong DHR, 46 x 46 mm. In May, 1996 she is alive and free of disease 23 years following primary surgery.

In each of these patients resurgence of growth of the malignant disease followed an immunosupressive life event or drug (Table 3). In the first case, a liver metastasis appeared five months after irradiation and steroid therapy. In the second, liver metastasis followed a heart attack and immunosuppressive treatment for up to 22 months[8-10]. In the third case, tumor growth followed severe endogenous depression, a condition recognized to be immunosuppressive and often to herald reactivation of long dormant cancer[11].

The rarity of metastases occurring more than 10 years after primary surgery is shown in Table 4 covering a patient observation period of 31

TABLE 3.— *Data on three patients from Ottawa General Hospital series with late nonregional metastases and no new primary tumor*

Sex	Age, yr	Primary tumor	Course	Max DHR, mm
M	58	Poorly differentiated adenocarcinoma, T2NO	Brain metastasis 11 yr cerebral irradiation and steroids Liver metastasis 11 yr 5 mo	20 x 7
M	44	Adenoid cystic carcinoma, T2NO	Myocardial infarction 6 yr Liver metastasis 12 yr	31 x 31
F	57	Adenocarcinoma, T2NO	Endogenous depression 7 and 12 yr Scalene-node metastasis 14 yr	55 x 35

DHR = delayed hypersensitivity reaction.

years. The eight patients from Ottawa who survived more than 10 years are included in this table; three of them had nonregional metastases discovered over a 19-month period, an incidence that is 18-fold greater than that reported for the six published series[12-17] shown in Table 4. Those six series are consistent with the overall occurrence of 2% from the combined series (X^2 = 5.02, df = 5, p = 0,41). Comparison of the occurrence rate of metastases after more than 10 years between the Ottawa experience (37.5%) and the experience of six series overall yields a highly statistically significant result (p = 0.0006 based on Poisson probability). Even if the comparison is made with the highest incidence reported (4.1%) the results remain significant (p = 0.005). The observed outcome is consistent with a relative-risk estimate of 18.75 (95% CL, range from 11.25 to 26.25) of nonregional metastases, based on our sample of eight patients surviving 10 years or more. The sample size of eight has a statistical power of 75% to detect a relative risk of 15 or more, at a type I error level of 5%. Hence our sample size, although small, is large enough to detect such a high relative risk of recurrence of nonregional metastases.

A more recent report[18] on the incidence of recurrence of adenocarcinoma or large cell anaplastic carcinoma in a large series has shown no local or nonregional recurrence after seven years, with a follow up of 12 years for some patients. Two patients in Ottawa have been seen with local recurrence after treatment with steroids.

Case 4. This was a 54-year-old woman who underwent right lower lobectomy for squamous-cell carcinoma (T1NO) in August 1976. She also received immunochemotherapy in the original trial. At 5 months she had a strong DHR to 100 µg of soluble squamous cell antigen (32 x 27 mm induration) but 6 months later this declined to the prevaccination level (10 x 9 induration) despite strengthening reactions to recall antigens. Since such a specific decline in reactivity had been seen before[19] to herald recurrence it prompted an opinion that she had local occult recurrence, since her chest x-ray was negative for tumor. She was followed closely for seven years during which time she developed chronic interstitial pneumonitis in each lung. In October 1984 she presented with a three-month history of fever, a 12.3 kg weight loss and marked changes on the chest x-ray film. Following a bronchial biopsy, a right middle lobectomy was done. Histologically there was widespread fibrosis, lymphocytic infiltration with lymphoid follicles and multifocal areas of severe bronchial dysplasia and carcinoma in situ. She received a six-month course of prednisone 40 mg/day. In February 1986 ill defined lesions were seen in the left upper lobe on the chest x-ray film and she died two months later. At necropsy much of the left upper lobe was airless because of tumor infiltration and there was a subpleural lesion in the left lower lobe. Mediastinal nodes were free of tumor.

Two points may be made: the patient had accelerated tumor growth after steroid therapy; the chronic interstitial pneumonitis and the histological

TABLE 4.— *Frequency of late nonregional metastases from six published series compared with that of the Ottawa Experience*

Source	No. patients surviving ≥ 10 yr	No. patients with metastases seen after 10 yrs	%
Belcher & Anderson, 1965[12]	143	2	1.4
Abbey Smith, 1970[13]	49	2	4.1
Abbey Smith, 1981[14]	151	4	2.6
Paulson & Reisch, 1976[15]	50	2	4.0
Temeck,Flehinger & Martini, 1984[16]	118	0	0
Kirsh et al, 1976[17]	53	1	1.9
Total	564	11	2.0
Ottawa series	8	3	37.5

picture seen in October 1984 could possibly reflect a host response to multifocal microscopic foci of disease, much as is seen in pulmonary tuberculosis.

Case 5. The second of these patients was a 43-year-old woman who had a right upper lobectomy for an adenocarcinoma T1NO in February 1980. One year after immunotherapy she had a strong DHR to 100 µg of adenocar-cinoma antigen (54 x 40 mm induration). She remained well until November 1988 when she complained of a 5.9 kg weight gain and a one-year history of asthma. A chest x-ray film showed no evidence of recurrence or metastases. After diagnostic challenge in the respiratory laboratory topical cortisone by aerosol and prednisone 10 mg orally, twice daily, were prescribed for one week. Her symptoms worsened and the therapy was repeated in January 1989. By July ipsilateral and mediastinal metastases were found. She died 10 years after the primary surgery. Necrosy revealed extensive adenocarcinoma in the remaining right lung and in the left lung.

Case 6. A 67-year-old man had a right penumonectomy in April 1981 for a large-cell anaplastic carcinoma (T2NO) measuring 8 x 6 cm. At one year postsurgery and immunotherapy he had a DHR of 23 x 20 mm induration to 100 µg of anaplastic antigen. During the following years his course was complicated by a mild left-sided stroke in 1982, a myocardial infarction in December, 1984 and again in 1987 accompanied by pneumonia. He died of acute bronchopneumonia on December 26, 1988. At necropsy an incidental finding was an 11 mm metastasis with anaplastic carcinoma in a contralateral hilar lymph node, very similar in morphology to the original primary tumor containing many mitoses. A scrupulous search failed to reveal a new primary tumor. Had this patient survived the metastasis should have become clinically apparent well after 8 years from the time of primary resection.

Following the publication of these findings[20] we convened the first international workshop on Cellular Immune Mechanisms and Tumor Dormancy in Ottawa in October, 1991. The aim of this workshop was to bring together basic scientists and clinicians from many fields who had either directly studied tumor dormancy or who had encountered it in their clinical experience. The proceedings were published in 1992 by CRC Press[21]. Those experiments which are relevant to our findings in lung cancer will now be summarized.

Suzanne Eccles[22] described experimental models where prolonged dormancy of tumors was induced and where immune mechanisms were implicated. Much of her earlier work was done in collaboration with the late Peter Alexander. In order to determine whether tumor cells exist in the body following excision of tumors that had been shown to have a low incidence of metastases two strategies were employed. *One*; postsurgical treatment with immunosuppressive agents. *Two*; bioassay of target organs (lung or lymph nodes). Following excision of the immunogenic rat sarcoma HSBPA all animals remained healthy for 1 1/2 - 2 months. In the succeeding 1 1/2 years 10% succumbed to lymphatic or hematogenous metastasis. If animals were subjected to whole body X-irradiation or chronic lymph drainage, with treatment initiated 1-30 days post tumor excision the incidence of metastasis was increased to between 30 and 58% and mean survival time was significantly decreased. Similarly, it was found that if cyclosporin A treatment was delayed until after excision of rat sarcoma MC24 the incidence of metastases rose from 0% to between 50 and 100%. Similar effects were obtained in a variety of rat and mouse sarcomas and in lymphoma L5178YE.

A sensitive bioassay was also developed to detect dormant tumor cells in such animals. Organs potentially harbouring dormant cells were removed from the host and transferred to immune-deprived animals. Sublethally-irradiated weanling rats would support the growth of very low cell inocula, being even more sensitive than athymic hosts. As few as 10-50 tumor cells in a whole organ, when inoculated intraperitoneally yielded progressively growing tumors in 100% of recipients. The bioassay protocol was as follows. Day 0: tumors implanted. Day 14: tumors excised. Day 28: blood, lung and lymph nodes bioassayed. Parallel groups of control animals were kept for survival assays. Lungs or lymph nodes were found to contain viable tumor cells in a high proportion of animals using this bioassay, not apparent in control animals.

Long-term tumor stasis induced by «immunotherapy».

Eccles asked whether tumor cells induced to secrete IL-2 following retroviral transfer and expression of an IL-2 CDNA might amplify a weak local antitumor response in a paracrine fashion.

It was found that three clones of the rat sarcoma HSN (marginally immunogenic) secreting different amounts of IL-2 showed reduced tumorigenicity and metastatic capacity related to their level of IL-2 secretion. The behavior of clones secreting an inactive form of human IL-2 was unaltered. Long duration growth stasis was observed for a proportion of IL-2 secreting tumors. In those tumors that regressed some recurred months later indicating a period of dormancy.

Treatment of human breast and squamous cell carcinoma lines grown as xenografts in athymic nu/nu mice with rat monoclonal antibodies to human EGF-R caused complete regression of a proportion of tumors. Dormant tumor cells were found in the scars of such regressed lesions at day 70, with control animals showing no subsequent growth.

Eccles concludes by stating that unequivocal evidence for tumor dormancy has been observed, in some cases undoubtedly induced by elements of the host immune response. She also showed data that antiendocrine treatments of rat mammary tumors could cause tumor stasis, with renewed growth on removal of the treatment.

Wheelock[23] reviewed immune regulation of a murine T-cell lymphoma dormant state. DBA/2 mice receive a subcutaneous inoculation of 1 x 10^6 viable L5178Y cells (a methylcholanthrene-induced syngeneic, non-metastatic T cell lymphoma line) on their ventral surface. The resulting nodule is excised 10 days later. Seven days later the mice are challenged intraperitoneally with 5 x 10^4 L5178Y cells, a dose which produces ascitic tumors and death in 100% of nonimmunized mice by the 27th day. In contrast, immunized mice remain clinically normal for weeks, with ascitic tumors developing at random, some as late as 340 days. This dormant state is a result of control by cytotoxic lymphocytes and macrophages with ultimately the emergence of a resistant clone of tumor cells. This immune reaction is dynamic, with tumor cells passing through the cell cycle, the net effect being the maintenance of a small population of tumor cells that are growing and dying, to give zero growth.

Stevenson et al[24] describe a model of tumor dormancy in a B-cell lymphoma, also studied by Uhr et al[25]. This is an important model for several reasons. First, in terms of relevance to our findings in non-small-cell lung cancer, dormancy can be induced by immunizing mice with a tumor specific cell surface antigen homogenized with Freund's complete adjuvant, given as 3 injections on days 0, 7 and 17. In our patients, the vaccine was given at monthly intervals for 3 injections. The specific antigen in B cell lymphomas is a surface immunoglobulin, an idiotypic IgM (IgMId). Dormancy in the murine BCL lymphoma can be induced by several strategies including cytoreductive therapy of mice with large tumor burdens and challenge of allogeneic chimeric mice or idiotype-immunized mice with BCL tumor. Dormant tumor cells were isolated from the spleens of the chimeric mice and the majority were shown to be noncycling; 80% were in G0 or GIA. This implies that an immune response can maintain a specific cell cycle blockade, as predicted by Hadfield in 1954[3]. More recently Racila et al[26] have published evidence that antibody to IgM is sufficient to induce a state of dormancy in this murine B cell. BCL tumor cells were injected into SCID mice passively immunized with antibody against different epitopes on IgM or IgD with or without idiotype (ID)-immune T lymphocytes. Results indicated that antibody to IgM is sufficient to induce a state of dormancy. Id-immune T cells by themselves had no effect on tumor growth but simultaneous transfer of anti-Id antibody and Id-immune T cells enhanced both the induction and duration of the dormant state. In vitro studies indicated that antibody to IgM induced apoptosis within hours and cell cycle arrest by 24 hours.

Taken together these animal studies show convincingly that cellular and hormonal mechanisms can induce and maintain dormancy, as suggested by Gordon Taylor[1] and Willis[2]. Contributors to the workshop then examined in detail animal and human studies that show surgery[27], anaesthesia[28] and perioperative blood transfusion[29, 30] all to be immunosuppressive for varying periods allowing a rational explanation of why the dormant state may be terminated by «surgical operation for some independent condition».

A recent contribution to understanding another important mechanism involved in maintaining the tumor dormant state has been reported by Holmgren et al and that is suppression of angiogenesis[31] reviewed by Folkman[32]. These authors studied dormant lung metastases under angioge-

nesis suppression in mice. Such metastases exhibited rapid growth when the inhibition of angiogenesis was removed. Tumor cell proliferation was not significantly different in dormant and growing metastases. However, tumor cells of dormant metastases exhibited a more than three fold higher incidence of apoptosis. The data from these experiments show that metastases remain dormant when tumor cell proliferation is balanced by an equivalent rate of cell death and suggest that angiogenesis inhibitors control metastatic growth by indirectly increasing apoptosis in tumor cells.

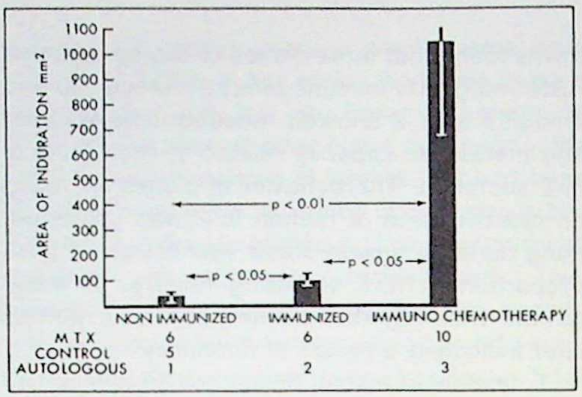

Fig. 1.— Reprinted from *Canadian Journal of Surgery* 1991; 34: 321-5, by permission of the publisher

Implication for the Future

Ideally a successful adjuvant therapy for cancer should kill every remaining cancer cell in the host, in the setting of minimal residual disease. This is probably a naive hope. In the adjuvant treatment of breast cancer, to date the most successful example of adjuvant chemotherapy for common solid tumors, local wound recurrence following adjuvant chemotherapy were not consistent with a constant growth rate but suggested a period of dormancy followed by a rapid growth phase[33]. Of 122 women followed, 104 received adjuvant chemotherapy. It has been suggested[34] that the observed dormancy following chemotherapy is secondary to the deprivation of the tumor of host derived stimulatory cytokines, markedly reduced by the immunosuppression seen following such chemotherapy.

The clinical and animal data strongly suggest that the dormant tumor state can be induced and maintained. The future development and use of cancer vaccines has recently been reviewed by Old[35] and Prehn[36]. Old suggests that the structural identification of tumor peptides recognized by human T cells and proteins and glycolipid antigens recognized by human antibodies opens the way to the rational development of immunogenic vaccines. Many questions need to be answered; what peptides or proteins provide the most effective immunogenic stimulus, what is the optimal adjuvant, can exogenous cytokines direct and augment the response, what are the advantages of viral delivery systems, will DNA vaccines be effective? Polyvalent vaccines containing peptides, proteins and glycolipids derived from several different gene products may well overcome tumor escape. Prehn cautions that in order to obtain a therapeutic response the increase in the immune reaction will need to be massive; a weaker response might facilitate tumor growth[37]. The strong DHR to lung cancer antigen that is induced by vaccinating using the strongest known adjuvant at the time of the clinical trials, lasting and maintained for more than a decade[6, 7] and shown in Cases 2, 3, 5, suggest that this is achievable. The strength of the induced DHR can be compared to the weak reaction seen in nonimmunised patients (Fig. 1). «Wild» antigens derived from allogeneic tumor specimens are unacceptable to the US Food and Drug Administration. Demanded are genetically engineered products, with batch to batch reproducibility and free of virus. With a large capital outlay such antigens could be produced and should be effective in inducing tumor dormancy in the adjuvant setting, with clinical benefit.

Acknowledgements: Dr. Jacob Karsh for editing the manuscript.

Resumen

Mecanismos inmunológicos y el estado de tumor dormido

Se discuten los mecanismos inmunológicos que afectan el estado de tumor dormido en base a las observaciones clínicas de un distinguido cirujano y de dos patólogos durante una vida de práctica médica. Ellos concluyeron que la presencia de tumores dormidos es el resultado de mecanismos inmunes que previenen el desarrollo

de metástasis microscópicas que preceden al tratamiento quirúrgico. Se presentan seis casos de cáncer de pulmón no a células pequeñas que fueron randomizados en un protocolo de inmunoterapia con adyuvantes. Tres pacientes presentaron metástasis a distancia recién a los 11, 12 y 14 años. Dos tenían metástasis regionales a los 9 años y en un paciente se encontró una pequeña metástasis en el ganglio hilar en la autopsia a los 7,6 años. En cada caso la proliferación metastásica fue precedida por un episodio de inmunosupresión o de quimioterapia. Se discuten los modelos experimentales de estado de tumor dormido y la evidencia surje claramente a favor de su inducción y mantenimiento por mecanismos inmunológicos tales como células en arresto mitótico, o proliferación celular equilibrada con muerte celular. Se concluye que futuras estrategias clínicas deberían intentar mantener las micrometástasis en estado de tumor dormido dentro del marco del uso de adyuvantes.

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The definition of tobacco smoking as a major health hazard in the Western world ranks with the discovery of the last century of the dangers of contaminated water supplies. It is also a demonstration of the wide hiatus between knowledge and wisdom, especially when profits tilt the balance, and of the small place science occupies in our political-economic ecology.

La definición de tabaquismo como un riesgo mayor para la salud en el mundo occidental se alínea con el descubrimiento del último siglo de los peligros de la contaminación en el abastecimiento de agua. Es también una demostración de la amplia separación entre conocimiento y sabiduría, especialmente cuando las ganancias inclinan la balanza, y del poco lugar que la ciencia ocupa en nuestra ecología político-económica.

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