

Clinical and Experimental Studies



Clinical and Experimental Studies

Appendix Three is a collection of references that pertain to some aspect of remission research. It is divided into three sections. “Immune Transfusion Studies” presents clinical studies in which blood or plasma from a person with evidence of cancer regression is transfused into another person with the same cancer in an effort to induce remission. This section contains 5 annotated references and 8 case reports.

The second section of this chapter, “Cellular Immunity,” contains 7 annotated references, 4 of which present experimental studies of the effects of blood lymphocytes from persons with progressive and regressive cancers on tumor tissue in-vitro.

The third section, “Other Clinical and Experimental Studies,” contains 16 annotated and 18 supplemental references. Three case reports are presented. The reports in the third section are primarily clinical, epidemiological, retrospective and prospective, or theoretical studies of the relationship of psychological variables to cancer survival.

From information contained in anecdotal reports, there appear to be similarities between the psychospiritual characteristics of people who experience remission and long-term survivors. For this reason, clinical studies that attempt to define characteristics of survivors are important to provide a more complete picture of the relationship between the mind and cancer remission.

Immune Transfusion Studies

Spontaneous Regression of Human Melanoma *Clinical and Experimental Studies*

SUMNER WC; FORAKER AG
Cancer 13(1): Jan-Feb 1960; 79-81

Extracted Summary

Serum from 2 patients with regression of proved melanoma metastases failed to influence the progression of Harding-Passey melanoma in BALB/c mice. It is believed that this failure is probably due to too wide variances in tumor types. Further immunological investigations of melanoma regression are suggested.

SELECTED CASE REPORTS

Patient R. R. was first seen in 1949 at the age of 30 and found at that time to have disseminated malignant melanoma in breast, groin, abdominal wall, and back. No definite primary site was discovered. On the left internal malleolus, however, there was an area of depigmentation. The patient stated that 3 years previously a mole had become infected and "dropped off." The diagnosis of metastatic melanoma has been confirmed by numerous pathologists. Some lesions were excised; others disappeared spontaneously, leaving zones of depigmentation of overlying skin very similar to that of the "primary lesion." Subsequently excised nodes showed degeneration of tumor and fibrosis. There has been no evidence of tumor since 1950. This case was reported by one of us (WC. S.) in 1953.

The second patient (J. H.) was first seen in 1952, at the age of 26, with disseminated melanoma. This patient stated that approximately 1 year before, he had had a pigmented lesion over the right scapular region removed by a doctor in his home town, who advised no other treatment at that time. The patient, when first seen by us in 1952, had multiple metastases occurring in the scar on his back, the right neck region, right axilla, left anterior chest wall, and left and right anterior abdominal wall. Biopsies of these areas were interpreted, by the same pathologist who reviewed R.R.'s slides, as showing metastatic melanoma. No definitive surgery was advised. The

patient was referred to the National Cancer Institute at Bethesda, Maryland, for observation and possible therapy. Various metabolic and biochemical studies were made with no unusual findings. Following his discharge from the National Cancer Institute Hospital, the patient returned to Jacksonville, Florida, and presented himself on numerous occasions with multiple recurrences in various parts of the body, which were excised. On June 1, 1954, he returned to the office with recurrences in the left parietal region and the left buttock region and an enlargement of the lymph nodes in the right axilla. 250 cc of R. R.'s blood, which was of the same type and compatible cross match with that of J. H. was given. Six weeks later he stated that on July 20, 1954, he noticed the "lumps" on his head and right thigh were disappearing. Within 6 weeks all lesions had disappeared or materially regressed. Three months later all had disappeared. Following this regression in the scalp, the overlying hair became white, while all the rest of his hair remained black. He remained free of disease until November, 1955, when a small metastasis was discovered in the proximal phalanx of the ring finger of the right hand. (On review of the history, the patient had complained of pain in this finger at the time the serum was given in 1954.) The finger was amputated and reported as showing metastatic melanoma with much central necrosis and fibrosis. The patient has remained free of further evidence of disease.

Surgical Management of Malignant Melanoma

TEIMOURIAN B; McCUNE WS
American Journal of Surgery 29(7): July 1963; 515-519

Extracted Summary

In this paper, the authors discuss the surgical management of malignant melanoma and advocate the early surgical removal of lesions of malignant melanoma.

As a part of this presentation, the authors discuss their experience with the use of immune transfusions as a possible treatment procedure for malignant melanoma. The authors present a brief description of an earlier study (Sumner and Foraker, 1960) in which a patient with malignant melanoma was transfused with the blood from a patient in spontaneous remission from malignant melanoma. Complete remission followed.

The authors repeated the procedure on a 29-year-old man with a melanoma of the shoulder with metastases to the lungs. This patient was transfused with the blood of a female patient who had survived without recurrence for ten years following removal of a melanoma of the back with bilateral axillary metastases. Over the next four months the lung metastases gradually diminished in size and almost disappeared. Brain metastases appeared, with hemiplegia. Following another immune transfusion the patient again improved until he was able to work. He died of melanoma one year later. At postmortem examination the lung metastases were only small areas of necrosis.

Host Defences in Burkitt Tumour

NGU VA

British Medical Journal 1: 1967; 345-347

Extracted Summary

The possibility that host factors or immunological agents play a part in the results achieved in the treatment of the Burkitt tumour has long been suspected. Thus Burkitt (1962), in East Africa, showed that adults living in regions where this lymphoma was prevalent did not suffer from the tumour, whereas adults who had come from non-endemic regions were apt to contract the lesion. Moreover, the overall long-term survivals achieved in the treatment of the Burkitt lymphoma are much better than those achieved with other lymphomas even with small doses of drugs. Regressions of the Burkitt lymphoma have even occurred when treatment was abandoned or refused.

Ngu (1965) suggested that, if host factors were involved in some of the remissions seen, such factors would theoretically be easier to detect in those who had had long remissions than in those who had succumbed early to their tumour. Such early deaths might be taken as presumptive evidence of failure or inadequacy of host defence factors, whatever the reasons for this failure might be. Hence it was decided to search for a humoral factor in patients with long remissions.

SELECTED CASE REPORTS

Case 1: A 4-year-old boy (blood group B, Rh-positive) was admitted to hospital on 2 September 1965, with a 20-day history of swelling of the left cheek and right upper eyelid and some respiratory difficulty. On examination he was a very ill child weighing 22 pounds (10 kilograms) with bilateral involvement of both maxillae and both mandibles by tumour masses. The maxillary tumour had ulcerated into the nostrils, from which a moderate amount of bleeding was observed. Nasal obstruction and extension of tumour into the mouth had rendered normal breathing difficult. A tracheostomy was therefore established on admission. The periorbital tissues were involved by tumour, more extensively on the right side than on the left. The rest of the physical examination did not reveal obvious tumour masses elsewhere in the body. X-ray examination of the facial bones showed extensive destruction of both maxillae and mandibles with displacement of the teeth (anarchie dentaire). There was loss of dental lamina dura. Biopsy examination of the tumour on the left cheek showed the presence of Burkitt tumour cells.

On 3 September 150 milliliters of immune plasma I

was transfused into the child. Next day he looked infinitely better, though he had a temperature of 102° F. (38.9° C.). The patient's general condition remained satisfactory, but his temperature continued to swing until 12 September, when it settled. Because of occasional epistaxes, however, and a haemoglobin of 6.9 gm/100 ml (47%), he was transfused with 350 milliliters of whole blood obtained from a local adult Nigerian who had not suffered from Burkitt tumour. On 12 September it was noticed that the jaw tumour was regressing fairly rapidly, and next day the serum uric acid had risen to 9.6 mg/100 ml. Throughout this period no cytotoxic drug had been given.

He remained well until 26 September, about three weeks after the plasma infusion, when it was noticed that the tumour in the left cheek had recurred. A week later it was 3 centimeters in diameter, and intravenous cyclophosphamide (10 mg/kg body weight) was started, being continued for five days, with complete regression of the tumour. He was discharged home on 29 October in reasonable health but having lost about 4 pounds (1.8 kilograms) in weight.

A week later he was readmitted with a history of

vomiting and listlessness. Examination showed a thin dehydrated child with a bed sore over the sacrum, moderate neck stiffness, paralysis of the third, fourth, sixth, and seventh cranial nerves, and a flaccid paraplegia of both legs. At lumbar puncture the pressure was raised, and when examined by phase contrast microscopy and tissue culture, his C.S.F. was found to contain viable Burkitt tumour cells in large numbers. X-ray examination of the spine showed a small paravertebral mass in the lower thoracic region. He was again treated with intravenous cyclophosphamide for 10 days without any change in his clinical condition, and he died on 5 December.

Necropsy showed only scars of healed lesions in the maxillae and renal cortex, where tumour masses had been. Viable tumour was present within the meninges and involved the cranial nerves at the base of the skull; histology showed only a Burkitt-cell "meningitis and encephalitis."

Case 2: A 4-year-old girl (blood group O, Rh-positive) was admitted to hospital on 19 January 1966 with a two-month history of swelling of the right cheek. She had a classical Burkitt tumour of the right maxilla and mandible, with extension of tumour into the parotid and right submental regions. She also had an enlarged lymph node in the right posterior triangle. A specimen of bone marrow from the right iliac crest showed gross invasion by Burkitt tumour cells; an x-ray film of facial bones showed destructive changes typical of Burkitt tumour; an intravenous pyelography revealed displacement of calices by an intrarenal deposit; and biopsy of the tumour disclosed Burkitt tumour cells.

On 20 January, after immune plasma II (group B, Rh-positive) was found compatible with the patient's red cells (group O, Rh-positive), she was given an infusion of 100 milliliters of the immune plasma. She was also started on prophylactic tetracycline, given for two weeks. On the fifth day after this she developed a swinging fever of up to 102° F. (38.9°C.), which persisted until the 14th day. Coinciding with the onset of the fever, the jaw tumour appeared to be somewhat larger and then became softer and more cystic in consistency. When the fever began to subside on the 14th day the tumour had become smaller and its cystic consistency more evident. The serum uric acid was at this time 17.9 gm/100 ml (4.9 gm/100 ml on admission).

When tumour regression had ceased, two weeks after the plasma infusion, a pint (500 milliliters) of fresh compatible blood from an adult Nigerian was transfused without any effect on the rest of the tumour. Cyclophosphamide (10 mg/kg intravenously daily) was also started. Further regression of the tumour was observed, as well as a continued general improvement in the clinical status of the patient. On the fifth day of chemotherapy she suddenly collapsed and died. Necropsy did not show any haemorrhages. Partly necrotic tumour tissue was present in the right cheek, lower cervical lymph nodes, and right femur. Histology of the cheek tumour showed few viable tumour cells, but an increase in the number of histiocytes. No satisfactory anatomical cause of death was found, and it was thought to have been due to hyperuricaemia consequent upon the drug-induced tumour destruction.

Evaluation of the Effect of Remission Plasma on Untreated Patients with Burkitt's Lymphoma

FASS L; HERBERMAN RB; ZIEGLER JL; MORROW RH JR
Journal of the National Cancer Institute 44(1): Jan 1970; 145-149

Extracted Summary

In a controlled study eight patients with untreated Burkitt's lymphoma were given plasma from patients with Burkitt's lymphoma in remission or from normal volunteers. Although the donor plasma was shown to have in-vitro antibody activity, no evidence for in-vivo anti-tumor activity was noted. This preliminary study does not confirm previous reports of in-vivo anti-tumor activity in the plasma of patients with Burkitt's lymphoma.

An Immunological Approach to the Therapy of Cancer?

HORN L; HORN HL
Lancet: Aug 28 1971; 466-469

Extracted Summary

Four patients in one family, all with clear-cell carcinoma of the kidney, are described. Patients number 2 and 4 have been symptom-free since nephrectomy. Patient number 3 was found to have

asymptomatic pulmonary metastases approximately a year after a nephrectomy. Patient number 3 has been receiving plasma transfusions from patient number 2, who has been plasmapheresed first weekly and then biweekly. Plasma transfusion/plasmapheresis technique involving patients number 2 and 3 has been successfully performed over a fifteen-month period with sustained remission in the recipient patient number 3 and no untoward effect on the donor patient number 2.

SELECTED CASE REPORTS

Case 1. Patient number 1, a 43-year-old physicist, presented with haematuria in January 1965. Intravenous pyelography revealed a lesion of the left kidney. Nephrectomy was performed. Pathological report was as follows: clear-cell carcinoma poorly differentiated with focal invasion of renal capsule, superior calyx and branch of renal vein. In May 1966, a chest radiograph showed metastatic lesions in the right lung. He was given radiation therapy to the lung and subsequently was treated with progesterone and prednisone. He responded poorly and died in December 1967.

Case 2. In November 1968, patient number 2, aged 77, a music teacher and father of patient number 1, presented with haematuria. Intravenous pyelography and cystoscopy revealed lesions of both the left kidney and the bladder. Nephrectomy was performed and the bladder lesion was fulgurated. The gross kidney specimen revealed renal-vein invasion; microscopic study disclosed the characteristic picture of clear-cell carcinoma; and the bladder tumour proved to be a transitional-cell carcinoma. Resection of the sigmoid colon had been undertaken in 1948 for an adenocarcinoma. There has been no evidence of recurrence of any of the malignant tumours. This patient has been the plasma donor in the current study with no apparent ill-effect.

Case 3. Patient number 3, a 43-year-old physician, a cousin of patient no. 1 and a nephew of patient number 2, was seen for a routine physical examination in January 1969. He was completely symptom-free, and physical examination was negative. The only positive finding was microscopic haematuria, one to three red blood cells per high powered field in one urine specimen. Intravenous pyelography revealed a lesion of the left kidney. Nephrectomy was performed and the kidney was found to contain clear-cell carcinoma. This tumour had not invaded the capsule of the kidney nor had it invaded the renal vein. Microscopic examination revealed the characteristic picture of a clear-cell carcinoma. A year later (February 1970) a metastatic survey showed what "appeared to be a solitary lesion" of the lung limited to the left upper lobe. Thoracotomy and left upper lobectomy were performed on February 21, 1970. At operation, multiple lesions of the left upper lobe were found and metastasis to regional lymph nodes was evident. A frozen section on a lymph node biopsy specimen revealed characteristic clear-cell carcinoma. Despite the evidence of multiple metastases with extensive regional lymph node involvement, lobectomy was performed. Some of the regional lymph nodes were removed but many considered

by the surgeon to be involved by tumour were left in situ. The lesions of the lung on microscopic examination also showed the characteristics of clear-cell carcinoma of the kidney. While the patient was in the recovery room it became apparent that there had been a collapse of the left lower lobe, and a second thoracotomy was immediately performed and the left lower lobe bronchus repositioned, resutured, and the left lower lobe re-expanded. An oncology consultation was obtained and a pessimistic opinion was rendered as to therapy and prognosis. Accordingly, it was decided that this was an ideal human experimental situation in which to attempt to determine whether patient number 2 (father of patient number 1 and uncle of patients 3 and 4) had a substance (or substances) in his plasma which might prove beneficial to patient no. 3. Both donor and recipient were of the same blood type (group A, Rh positive). Accordingly, on March 12, 1970, plasma transfusions with the plasma from two units of blood were initiated on a weekly basis with patient number 2 as the donor and patient number 3 as the recipient. This was done by double plasmapheresis as follows: Blood was drawn from the donor's antecubital vein. The 500 milliliters of blood removed by each phlebotomy was centrifuged at 4,500 r.p.m. in a refrigerated centrifuge for ten minutes. Separated plasma was extracted to a point approximately 1-2 centimeters above the packed red cells in order to avoid the buffy coat. After returning the first unit of packed cells to the donor, a second phlebotomy was performed to obtain a second unit of whole blood, and the above procedure was repeated. Bags were from Fenwal PA-220, each bag containing 75 milliliters of 0.8% citric acid (hydrous), 2.2% sodium citrate (hydrous), and a 2.45% dextrose (hydrous). This therapy was continued weekly from March 12, 1970, until June 11, 1970, at which time there was a slight drop in the donor's serum albumin and it was decided to continue the therapy on a biweekly schedule for the safety of the donor. This schedule has been continued up to the present time with patient number 2, the donor, and patient number 3, the recipient, both remaining in good health. Repeated search for recurrence of the tumour in patient number 3 has proved negative. The last chest radiograph, in May 1971, is entirely negative for metastases, and the patient feels completely well. After a fifteen-month period of observation there is no evidence of recurrence manifested by symptoms, physical findings, or radiographic examinations.

Case 4. Patient number 4, aged 46, a businessman and nephew of patient no. 2 and cousin of patients number 1 and 3, was persuaded to have a complete

physical examination and intravenous pyelography. Physical examination (March 1970) was negative, but intravenous pyelography revealed a neoplastic lesion of the lower pole of the right kidney. Nephrectomy was performed in April 1970, and the right kidney removed. On pathological examination of the tumour there was

disagreement among the pathologists, some calling it a hypernephroid (clear-cell) cystadenoma, others calling it a clear-cell cystadenocarcinoma. Metastatic survey prior to surgery and one year later have been completely negative, and patient is in apparent good health.

Cellular Immunity

Studies on Cellular Immunity to Human Neuroblastoma Cells

HELLSTRÖM I; HELLSTRÖM KE; BILL AH; PIERCE GE; YANG JPS
International Journal of Cancer 6: 1970; 172-188

Extracted Summary

A colony inhibition technique was used to demonstrate immune reactions mediated by peripheral blood lymphocytes against tumor-associated (specific?) antigens of human neuroblastomas. Lymphocytes from all of 11 patients carrying actively growing neuroblastomas, as well as lymphocytes from all of 11 patients who were clinically symptom-free after therapy for neuroblastomas, inhibited colony formation of plated neuroblastoma cells. They did not inhibit normal skin fibroblasts derived from the same patients as the tumor cells. A specific colony inhibition of neuroblastoma cells was also seen with lymphocytes from 12 of 16 mothers of children with neuroblastomas and with lymphocytes from some fathers and siblings of such patients. No specific inhibition of neuroblastoma cell colony formation was seen with lymphocytes from patients not having neuroblastomas or from healthy subjects.

Serum from six of six patients with progressively growing neuroblastomas, but from none of our four patients who were clinically symptom-free after treatment for such tumors, could block lymphocyte-mediated colony inhibition of plated neuroblastoma cells. It is suggested that the former sera contained antibodies which could mediate an efferent form of immunological enhancement.

Blocking of Cell-Mediated Tumor Immunity by Sera from Patients with Growing Neoplasms

HELLSTRÖM I; SJÖGREN HO; WARNER GA; HELLSTRÖM KE
International Journal of Cancer 7: 1971; 226-237

Extracted Summary

Blood lymphocytes from tumor patients can specifically destroy cultivated neoplastic cells of the same histological origin as the tumors of the lymphocyte donors, irrespective of whether or not the donors have symptoms of growing tumor.

The purpose of the present study was to investigate whether sera from tumor patients could block the cytotoxic effect of lymphocytes immune to the specific antigens of the respective neoplasms. A wide variety of tumors were included in the tests, namely malignant melanomas, carcinomas of the colon, breast, ovary, endometrium, kidney, cervix uteri, lung, larynx, bladder, Fallopian tube, lip, seminomas and sarcomas.

Sera from 67 out of 81 patients with growing neoplasms were found to block the cytotoxic

effect of specifically immune lymphocytes. A blocking effect was seen both when the tumor cells, lymphocytes, and sera were derived from the same patients, and when the lymphocytes and sera were taken from different donors who had the same types of tumor as the target cells. No blocking was seen when the same sera were tested on tumors of histological types other than those of the respective serum donors.

A blocking serum activity was seen in only three of 19 patients who were symptom-free after tumor therapy. The findings thus suggest that there is a correlation between tumor growth in vivo and the presence of a blocking serum activity in vitro.

Demonstration of Cell-Mediated Immunity to Human Neoplasms of Various Histological Types

HELLSTRÖM I; HELLSTRÖM KE; SJÖGREN HO; WARNER GA

International Journal of Cancer 7: 1971; 1-16

Extracted Summary

Peripheral blood lymphocytes from a total of 373 tumor patients were tested by either a colony inhibition or a cytotoxicity test for cell-mediated immunity against human neoplasms of various histological types. Lymphocytes from 51 of 59 patients studied (88%) either reduced colony numbers formed by plated autochthonous tumor cells or were cytotoxic to them, and lymphocytes from 78 of 87 patients tested (89%) had a similar effect on allogeneic tumor cells of the same histological type as those of the lymphocyte donors. Evidence indicating antigenic cross-reactivity between tumors of the same histological type was obtained for the following seven groups of neoplasms: malignant melanomas, carcinomas of the colon, breast, testis, endometrium and ovary, and various sarcomas. Lymphocytes affecting tumor cells had no effect on normal cells from the same patient, or on cells from other types of neoplasms than the target cells under study.

The degree of cell-mediated immunity, as detectable with the techniques employed was approximately the same in patients having active neoplastic disease as in patients who were clinically symptom-free. Eleven of 12 patients who were tested after having been symptom-free for more than 2 years had a lymphocyte-mediated anti-tumor immunity.

Immunity to Neuroblastomas and Melanomas

HELLSTRÖM KE; HELLSTRÖM I

Annual Review of Medicine 23: 1972; 19-38

Extracted Summary

The authors review studies on immune reactions to tumor-associated antigens (TAA) of two types of human neoplasms, neuroblastomas and malignant melanomas. The reason for choosing these tumors is that they belong to the few human neoplasms which undergo occasional spontaneous regressions (indicating that they may be immunologically rejected by their hosts), and that they are among those most investigated with respect to both cell-mediated and humoral immune reactions against TAA. Knowledge provided by studying immunity to these neoplasms may help us to understand better host immunological defenses against other human tumors as well.

Clinical evidence for host-mediated immune reactions against neuroblastomas and melanomas is presented, and observations reviewed which show cell-mediated immune reactions against these tumors.

The authors discuss some of the clinical characteristics of neuroblastomas and malignant melanomas. The frequency of regression of neuroblastomas varies between different clinical series from a conservative figure of 1-2 percent (Gross RE et al., *Pediatrics* 23 (1959) 1179-1191) up to 16% (Koop CE et al., *Surgery* 38 (195), 272-278). It shows an interesting age distribution with regression being relatively common in children less than two years old at the time of diagnosis but extremely

rare later. Complete and permanent regressions of melanomas are relatively rare, the incidence in several series being less than 1% (Everson and Cole, Spontaneous Regression of Cancer, 1966). However, partial and temporary regressions are seen relatively frequently (5-15%).

There is some suggestive but very inconclusive clinical evidence that immunotherapy with plasma, blood, or lymphocytes from cured patients can be beneficial. A few striking examples may be worth mentioning: One patient who had melanoma with subcutaneous metastases became tumor-free following inoculation of 250 milliliters of blood from another patient whose melanoma had disappeared spontaneously (Sumner WC, Foraker AG *Cancer* 13 (1960) 79-81). Another patient had two temporary remissions of melanoma, metastasized to lung and brain, following two episodes of treatment with plasma from another patient who had been tumor-free 10 years after therapy for melanoma (Teimourian B, McCune WS *Surgery* 29 (1963) 515-519). A third patient with metastasized melanoma had undergone a spontaneous remission shortly following blood transfusion (McCredie J, Unpublished observations cited in Everson and Cole). Furthermore, inoculation of leukocytes from patients immunized against melanoma cells has occasionally led to tumor regression (Nadler SH, Moore GE, *Annals of Surgery* 164 (1966) 482-490; Krementz ET, *Annals of Surgery* 172 (1970) 747-748).

Immune Phagocytosis In Vivo of Human Malignant Melanoma Cells

THE TH; EIBERGEN R; LAMBERTS HB; OLDHOFF J; PLOEG EVD; KOOPS HS; NIEWEG NO
Acta Medica Scandinavica 192(1): Jul-Aug 1972; 141-144

Extracted Summary

Phagocytosis of tumour cells has been observed on imprint preparation from a lymph node metastasis removed from a patient with malignant melanoma. This observation was made when the patient developed a relapse after a spontaneous remission lasting nearly three years. Material from 37 other melanoma patients without a history of tumour remission was studied. Only four showed some degree of tumour phagocytosis. It could be demonstrated by means of the immunofluorescence technique that the freshly biopsied tumour cells were covered with immunoglobulins. After these immunoglobulins had been eluted from the tumour into solution with citrate buffer pH 3.2 they could react when tested by the indirect immunofluorescence technique with cultured melanoma cells. Furthermore these eluted antibodies were shown to induce phagocytosis in-vitro of cultured autologous melanoma cells by heterologous macrophages. The failure of immune elimination of tumour cells and the significance of macrophages in this phenomenon is discussed in relationship to the observed development of a diminished skin reactivity to dinitrochlorobenzene and a normal response of patient's lymphocytes to phytohaemagglutinin in-vitro.

Comparison of "Host Cell Infiltrates" in Patients with Follicular Lymphoma with and without Spontaneous Regression

STRICKLER JG; COPENHAVER CM; ROJAS VA; HORNING SJ; WARNKE RA
American Journal of Clinical Pathology 90(3): Sep 1988; 257-261

Extracted Summary

The "host cell infiltrates" in five patients with low-grade follicular lymphoma who had spontaneous regression without therapy were studied with the use of immunohistochemical methods applied to frozen sections. These infiltrates were compared with the "host cell infiltrates" in six patients with follicular lymphoma with progressive disease. The group with progressive disease was selected to be similar to the group with spontaneous regression in age, sex, histologic characteristics, and stage of disease. The patients with spontaneous regression had significantly more T-

helper cells in the host cell infiltrate than the control patients. There were no statistically significant differences between the two groups in numbers of cytotoxic/suppressor T-cells, macrophages, Tac-positive cells, Leu-7-positive cells, or proliferating cells.

Spontaneous Regression of Neuroblastoma

An Experimental Approach

BOLANDE RP

Pediatric Pathology 10(1-2): 1990; 195-206

Extracted Summary

The phenomenon of spontaneous regression of neuroblastomas has intrigued oncologists and pathologists for many years. Neuroblastoma regression occurs most demonstrably and undeniably by cytodifferentiation to ganglioneuroma. However, neuroblastoma may also regress by complete cytolysis, leaving either fibrocalcific residua or no trace whatsoever. Regression of neuroblastoma occurs most often in the early months of life, particularly with congenital disseminated form (Stage IV-S).

Experimental studies as to the possible mechanisms of spontaneous regression of neuroblastoma are limited. Outstanding work in this field was carried out by the Hellströms (Hellström et al., *International Journal of Cancer* 6 (1970) 172-188; NCI Monograph 44 (1976) 131-134). They showed that lymphocytes of patients with neuroblastoma were cytotoxic to neuroblastoma cells but that blocking serum antibodies to tumor antigens would often mask these antigens and thus protect these cells from the cell-mediated cytotoxic effect of these lymphocytes. They concluded that spontaneous regression was probably due to immune mechanisms.

The cytolytic activity of normal pregnancy serum was first studied on murine cancer cells and shown to be the result of a natural IgM antibody that binds to cell surfaces and activates complement. Both the classical and alternative pathways of complement are involved. It was then shown that certain human neuroblastoma cell lines, to the exclusion of other human cancers, react to the same system. It is proposed that this system may play a role in the cytolytic form of spontaneous regression of neuroblastoma.

We showed that the serum system responsible for cytolysis of murine cells did indeed consist of a natural IgM "antibody" and complement. (The designation antibody is tentative in the absence of any clearly defined antigens.) We were then in a position to see if this system was operative in human cancer cell lines. We began a study of human cancers, focusing on neuroblastoma. This report is a synopsis of these experiments.

Other Clinical and Experimental Studies

A Possible Relationship Between Psychological Factors and Human Cancer

BLUMBERG EM; WEST PM; ELLIS FW

Psychosomatic Medicine 16(4): 1954; 277-290

Extracted Summary

A comparison has been made of the personality characteristics of cancer patients with rapidly advancing disease and similar cases in which the period of survival was far longer than the average expectancy. The psychological differences between patients in these two extreme clinical groups

were of such magnitude that in a significantly high percentage of cases they were readily detectable from the results of a single, relatively simple, objective test, the Minnesota Multiphasic Personality Inventory. The data obtained suggest that long standing, intense emotional stress may exert a profoundly stimulating effect on the growth rate of an established cancer in man. The major differentiating features of the psychological data are defined, and the possible significance of the findings in relation to host resistance is discussed.

Two cases are reported, one of which is presented below. The author comments that the results of this patient's MMPI are consistent with the clinical facts of this case. That is, the three criteria associated with rapid growth of the neoplasms in this study (high defensiveness or the appearance of serenity in the presence of deep inner distress, unrelieved anxiety or depression, and abnormal inability to decrease anxiety through outward action) were absent.

SELECTED CASE REPORT

This 42-year-old white male truck driver, G. H., developed pulmonary coccidioidomycosis in April 1947. Diagnosis was established by sputum culture following a small hemoptysis. The patient never had other symptoms and the lesion became quiescent.

Incidental findings during this first hospitalization were generalized lymphadenopathy, liver enlarged two finger-breadths below the costal margin, and firm splenic enlargement to the level of the umbilicus. Entrance blood counts showed: red blood count of 4.1 million and white blood count of 78,000 cells with 83% mature lymphocytes. Because of this, a bone marrow examination was

done which showed the typical picture of chronic lymphatic leukemia. Army records obtained after establishment of the diagnosis showed the presence in 1945 of "generalized adenopathy and splenomegaly."

At no time has the patient ever received treatment for his leukemia. He has continued to be asymptomatic and, as of March 1953, is working full time. He still evidences adenopathy, splenomegaly, and hepatomegaly. A recent blood count showed RBC 4.65 million and WBC 163,000 with 94% lymphocytes.

Duration: 6 years since diagnosis; probably at least 8 years since first manifestations.

Psychosocial Analysis of Cancer Deaths

WEISMAN AD; WORDEN JW

Omega 6(1): 1975; 61-75

Extracted Summary

In addition to biological activity and cancer treatment, psychosocial considerations may influence both the quality of survival and its length. The investigators used information from psychological autopsies of cancer deaths, and correlated observed survival (measured in months beyond expected survival) with psychosocial findings. Patients who lived significantly longer tended to maintain cooperative and mutually responsive relationships, especially towards the end of their lives. Patients with death wishes, depression, apathy, and long-standing mutually destructive relationships survived for shorter periods than expectable. Why longevity occurs in some patients, but not in others, may be related to different traits which create alienation in personal life and in caretaking staff as life draws to a close. More assertive patients ask for and get better attention and services, and, as a result, may live longer and die better deaths.

Psychological Response of Patients Cured of Advanced Cancer

KENNEDY BJ; TELLEGEN A; KENNEDY S; HAVERNICK N

Cancer 38(5): Nov 1976; 2184-2191

Extracted Summary

Psychologic testing was performed in 22 patients with advanced cancer (breast, endometrium, testis, lymphoma) who had undergone a complete remission that had been maintained for 5 to 20 years since the last therapy. The reaction to the probability of being cured was measured. The

patients' overall attitude was very positive towards life and the future. They had a greater appreciation of time, life, people, and interpersonal reactions. They were less concerned about the nonessentials of life. It appeared that recovery from advanced cancer was a good experience for character development.

SELECTED CASE REPORTS

Case 1: In 1957, a 51-year-old woman had an inoperable carcinoma of the breast and pleural effusion containing cancer cells. Treatment with nonenteric coated diethylstilbestrol, 5 milligrams three times per day orally, resulted in regression of the primary tumor and disappearance of the pleural effusion. Local recurrence occurred 18 months later and a total hypophysectomy was performed. The recurrent disease disappeared. Eighteen years after the initial diagnosis, there still is no evidence of cancer. She is now 69 years old.

Case 2: In June 1954, a 26-year-old woman had a mass in the left breast, an ovarian mass, a pathologic fracture of the left femur neck and an osteolytic lesion of the vertex of the skull. Histologic evaluation

of a biopsy of the breast mass and removal of both ovaries revealed Hodgkin's disease.

Radiation in a 600 R dose in air were given to the left femur. Nitrogen mustard, 6 milligrams intravenously (i.v.) daily for 4 days was given in June and October, 1954. The palpable tumor masses disappeared. In March, 1955, radiotherapy to the left femur was given in a total tumor dose of 1960 R. Two further courses of nitrogen mustard were given in April, 1955 and May, 1957. The x-rays all showed new bone or recalcified bone.

The patient refused to return to a doctor until 1972. Examination then revealed the left leg to be shorter than the right. She remains well to date. She was 47 years old at the time of interview in this study.

Psychological Coping Mechanisms and Survival Time in Metastatic Breast Cancer

DEROGATIS LR; ABELOFF MD; MELISARATOS N

Journal of the American Medical Association 242(14): Oct 5 1979; 1504-1508

Extracted Summary

Thirty-five women with metastatic breast cancer received a battery of baseline psychological tests; results were correlated with length of survival. Patients who died in less than one year from baseline were categorized as short-term survivors, while patients who lived for one year or longer were assigned to the long-term survivor group. The long-term survivors were more symptomatic overall, with particular elevations on measures of anxiety and alienation, and substantially higher levels of dysphoric mood (e. g., depression, guilt) than the short-term survivors. Short-term survivors revealed significantly lower levels of hostility, with higher levels of positive mood. Treating oncologists perceived the long-term survivors to show significantly poorer adjustment to their illnesses than the short-term survivors, and an interviewer's ratings indicated that long-term survivors had significantly poorer attitudes toward their physicians. Measures of clinical status and demographic data revealed few differences between the two groups.

Psychological Response to Breast Cancer: Effect on Outcome

GREER S; MORRIS T; PETTINGALE KW

Lancet ii: Oct 13 1979; 785-787

Extracted Summary

A prospective, multidisciplinary, 5-year study of 69 consecutive female patients with early [T_{0,1} N_{0,1} M₀] breast cancer was conducted. Patients' psychological responses to the diagnosis of cancer were assessed 3 months postoperatively. These responses were related to outcome 5 years after operation.

Recurrence-free survival was significantly common among patients who had initially reacted

to cancer by denial or who had a fighting spirit (15/20, 75%) than among patients who had responded with stoic acceptance or feelings of helplessness and hopelessness. (13/37, 35%)

Patients were interviewed with a structured interview schedule, and they completed standard psychological tests. Where possible, husbands or close relatives were interviewed separately to verify information elicited from patients. Psychological response to breast cancer was assessed 3 months after operation by asking patients how they perceived the nature and seriousness of their disease and how their lives had been affected by it. The psychological response was categorised according to patients' verbatim statements and accompanying mood.

Of the 67 patients in the original sample, 33 (49%) were alive and well with no sign of recurrence, 16 (24%) were alive but had had metastases (there were no patients with only local recurrence), and 18 (27%) had died of breast cancer. (2 had died from disorders other than cancer, 1 suicide, 1 myocardial infarct). Of the women who died, 88% (14/16) initially reacted with stoic acceptance or helplessness/hopelessness, whereas only 46% (13/28) of the women who remained alive and well demonstrated these reactions.

Psychological Intervention in the Treatment of Cancer

SIMONTON OC; MATTHEWS-SIMONTON S; SPARKS TF
Psychosomatics 21: 1980; 226-233

Extracted Summary

In a preliminary study of the effects of psychological intervention in the treatment of advanced cancer, it was found that patients so treated survived up to twice as long as would have been expected based on national averages. Better patient motivation, greater confidence in the treatment, and overall positive expectancy are thought to have contributed to the results. An educational model has been developed employing the psychological processes used in the study, and further investigations are under way to assess the effect of the patient's mental health on the course of cancer.

The Biological Correlates of Psychological Responses to Breast Cancer

PETTINGALE KW; PHILALITHIS A; TEE DEH; GREER S
Journal of Psychosomatic Research 25(5): 1981; 453-458

Extracted Summary

A prospective, multidisciplinary, 5-year study of 69 consecutive women with early breast cancer was conducted. Patients' psychological responses to the diagnosis were assessed 3 months postoperatively and correlated with various histological, mammographic, hormonal and immunological investigations performed preoperatively and at 3 months postoperatively.

There was no statistically significant association between the type of psychological response and any of the biological measures studied pre-operatively. There is, therefore, no evidence that biological factors have biased the composition of the groups and accounted for observed differences in outcome.

Serum levels of IgM, performed 3 months postoperatively, however, were significantly higher in patients who showed denial compared to those who responded with fighting spirit ($p < 0.02$) or stoic acceptance ($p < 0.02$). Also patients who showed fighting spirit had significantly lower serum levels of IgG than those who showed stoic acceptance ($p < 0.025$).

The mechanisms by which such immunoglobulin changes could influence survival in cancer remain hypothetical. A greater understanding of the neuroendocrine control of the immune system and much more sophisticated measurements will be needed to elucidate such mechanisms.

Mental Attitudes to Cancer: An Additional Prognostic Factor

PETTINGALE KW; MORRIS T; GREER S; HAYBITTLE JL

Lancet: Mar 30 1985; 750

Extracted Summary

In 1979, the authors reported the results of a prospective, multidisciplinary study of women with early breast cancer, which indicated that psychological responses to cancer diagnosis, assessed 3 months postoperatively, were related to outcome 5 years later (Greer HS et al., *Lancet* (1979) 785-87).

Recurrence-free survival was significantly commoner among patients who reacted to cancer by denial or "fighting spirit" than among patients who responded with stoic acceptance or feelings of helplessness or hopelessness. There was no evidence that this finding was due to initial biological differences, since these patient groups were similar in terms of clinical stage, approximate tumour mass, histological grade, mammographic appearance, and hormonal and immunological profiles (Pettingale KW et al., *Journal of Psychosomatic Research* 25 (1981) 453-458).

Now, ten years since our cohort of patients was recruited, we have re-examined the association between psychological response and outcome. Although there was a higher mortality rate in the second than in the first 5 years, a favourable outcome is still commoner among those whose responses were categorized as fighting spirit and denial (11/20, 55%) than among those who showed stoic acceptance or a helpless/hopeless response (8/37, 22%).

These findings should still be interpreted cautiously since the study is small and because most patients were treated by simple mastectomy as part of the King's/Cambridge Breast Trial, and thus histological examination of axillary nodes was not available in all patients. However, the second reservation may be of less importance than previously thought since a recent study of long-term survivors of breast cancer has shown that the prognostic influence of axillary node metastases and tumour size is almost completely confined to the first five years (Fentiman IS et al., *British Medical Journal* 289 (1984) 1108-1111).

The effect of mental attitude is independent of all the other prognostic factors examined and the possibility that our earlier findings were an artefact of incomplete staging is thus virtually excluded by this time factor.

The Prognostic Significance of Psychosocial Factors in Women with Breast Cancer

HISLOP TG; WAXLER NE; COLDMAN AJ; ELWOOD JM; KAN L

Journal of Chronic Diseases 40(7): 1987; 729-735

Extracted Summary

One hundred and thirty three recently diagnosed breast cancer patients completed a self-administered questionnaire which measured 16 psychosocial variables. After 4 years, three variables (expressive activities at home, extroversion, low anger) were significant prognostic factors for overall survival independent of clinical and other psychosocial factors; likewise three variables (expressive activities at home, expressive activities away from home, low cognitive disturbance) were significant independent prognostic factors for disease-free survival. These findings support the prognostic importance of the social emotional network.

An Intensive Psychoimmunologic Study of Long-Surviving Persons with AIDS

Pilot Work, Background Studies, Hypotheses, and Methods

SOLOMON GF; TEMOSHOK L; O'LEARY A; ZICH J
Annals of the New York Academy of Sciences 496: 1987; 647-655

Extracted Summary

In this paper, the authors present their preliminary biopsychosocial findings with long-term survivors of AIDS. An analysis of California AIDS patients survival (as of May 1986) indicates that 50% will survive one year after diagnosis, 30% for two years, and 2% after five years. The aim of the study is to study exceptional AIDS survivors to determine in what ways they are different from others whose life expectancy more closely conforms to the average life expectancy of AIDS patients (from 2 to 18 months depending on which form the disease takes). This pilot study utilized structured psychosocial interviews, weekly self-report analysis questionnaires, weekly group meetings which included immunologic analyses of blood samples, skin conductance, respiration, heart rate and finger temperature measurements to monitor the AIDS survivors in the study.

Information from studies in the related areas of psychosocial oncology, behavioral medicine, psychoimmunology, and pilot interviews with PWA (persons with AIDS) survivors was used to formulate hypotheses and design the study. It was hypothesized that long-term survivors (1) perceived the physician as collaborator; (2) had a sense of responsibility for their own health, felt they could influence the disease process, and did not see AIDS as a death sentence; (3) had a commitment to life; (4) had a sense of meaningfulness and purpose; (5) found new meaning as a result of the disease; (6) had a prior experience with life-threatening illness or serious life situation; (7) received useful information from a person with AIDS shortly following diagnosis; (8) was altruistically involved with other AIDS patients; and (9) altered their lifestyle and learned to "nurture" themselves.

The paper defines the hypotheses formulated and briefly describes the relevant studies used and the results of the pilot study. The authors suggest that studies of this type may provide clues that can serve as the basis of "biopsychosocial" intervention studies.

Personality, Stress and Cancer: Prediction and Prophylaxia

EYSENCK HJ
British Journal of Medical Psychology 61: 1988; 57-75

Extracted Summary

This paper reports results from three prospective studies, in which probands were followed over periods of 10 years, before inquiring about death and cause of death. Personality inventories were administered at the beginning of the 10-year period, as were questions concerning smoking, drinking, medical diseases, etc. It was found that personality variables were much more predictive of death from cancer or cardiovascular disease than was smoking, and that different personality types were susceptible to either of these two diseases. Personality type was defined in terms of different ways of dealing with interpersonal stress, and it was found that stress was a very potent cause of death, in the sense that stressed probands had a 40% higher death rate than non-stressed probands.

Survival Hazards Analysis in First Recurrent Breast Cancer Patients: Seven-Year Follow-Up

LEVY SM; LEE J; BAGLEY C; LIPPMAN M
Psychosomatic Medicine 50: 1988; 520-528

Extracted Summary

The purpose of this study was to identify predictors of survival time in first recurrent breast cancer patients, including psychologic as well as biologic factors. Beginning in 1979, 36 women being treated at the National Institutes of Health for histologically proven recurrent disease were enrolled in this prospective study. At the time of data analysis, 24 had died from their malignancy. Through the use of a Cox proportional hazards model, four factors significantly entered the equation predicting survival time in the sample: Patients with a longer disease-free interval, who expressed more joy at baseline testing, who were predicted to live longer by their physicians, and who had fewer metastatic sites tended to live longer with recurrent disease than others in the sample ($X^2 = 22.9$, $p < 0.0001$). Findings from recent clinical and animal studies suggest that regulatory systems within the organism are linked and potentially influence one another. This study has demonstrated that factors at a number of levels, behavioral as well as biologic, need to be considered in accounting for disease outcome variance.

Effect of Psychosocial Treatment on Survival of Patients with Metastatic Breast Cancer

SPIEGEL D; KRAEMER HC; BLOOM JR; GOTTHEIL E
Lancet 1: Oct 14 1989; 888-891

Extracted Summary

The effect of psychosocial intervention on time of survival of 86 patients with metastatic breast cancer was studied prospectively. The 1-year intervention consisted of weekly supportive group therapy with self-hypnosis for pain. Both the treatment ($n=50$) and control groups ($n=36$) had routine oncological care. At 10-year follow-up, only 3 of the patients were alive, and death records were obtained for the other 83. Survival from time of randomisation and onset of intervention was a mean 36.6 (SD 37.6) months in the intervention group compared with 18.9 (10.8) months in the control group, a significant difference. Survival plots indicated that divergence in survival began at 20 months after entry, or 8 months after intervention ended.

Most striking was the difference in survival from time of randomisation, when intervention began, until date of death. Survival time for the treatment group was significantly longer compared with controls. In addition the interval from first metastasis to death was significantly longer for the group randomised to treatment. Thus the intervention group lived on average twice as long as did controls.

Psychosocial Factors of Preserving Health?

*Prospective Studies of Breast Cancer, Bronchial Cancer
and Fibrocystic Mastopathy*

WIRSCHING M; DRINGS P; GEORG W; HOFFMANN F; RIEHL J; SCHLAG P; SCHMIDT P
Psychotherapie, Psychosomatik, Medizinische Psychologie 40(2): Feb 1990; 70-75

Extracted Summary

Do psychosocial factors affect the development of health? 156 patients were interviewed and tested before a breast biopsy or before the initial medical treatment of lung cancer. Multiple regressions were used to examine the influence of age, diagnosis (tumor stage) and different psychosocial

parameters as dependent variables, the development of health after 2 or 5 years as independent variables. The breast biopsy group (n = 52) shows five psychological variables being effective in a positive (health promoting) manner: autonomy, emotional outlet, expression of one's needs, family support, lack of life stress. In lung cancer (n = 104) the development of health 2 years after diagnosis is only influenced by the type of tumor (small cell versus non-small cell) and by the initial tumor stage. A structural equation model (LISREL) shows for the first 3 months of illness that almost exclusively biological variables have an influence on psychological variables. Despite this family dynamics had a moderate effect on the patient's general well-being (Karnofsky-Index).

Creative Novation Behaviour Therapy As A Prophylactic Treatment for Cancer and Coronary Heart Disease: Part I—Description of Treatment

GROSSARTH-MATICEK R; EYSENCK HJ

Behavior Research and Therapy Newsletter 29(1): 1991; 1-16

Extracted Summary

This paper describes a novel method of behaviour therapy applied to cancer-prone and coronary heart disease-prone patients in a prophylactic manner, to reduce the probability of their dying of cancer or coronary heart disease. The treatment can also be applied to patients already suffering from cancer in order to prolong their lives. The methods used are described in considerable detail, together with the rationale leading to their adoption. In Part II of this paper are the results of several studies showing that the methods are surprisingly successful in preventing death in cancer-prone and coronary heart disease-prone probands, and prolonging life in patients already suffering from terminal disease.

Creative Novation Behaviour Therapy As A Prophylactic Treatment for Cancer and Coronary Heart Disease: Part II—Effects of Treatment

EYSENCK HJ; GROSSARTH-MATICEK R

Behavior Research and Therapy Newsletter 29(1): 1991;17-31

Extracted Summary

In this article we consider the effectiveness of creative novation behaviour therapy in preventing cancer and coronary heart disease in disease-prone probands, and also its effectiveness in extending life for patients suffering from terminal cancer. In all cases, suitably matched controls are provided as part of the general methodology, and results are reported to testify to the effectiveness of the therapy, whether administered as long-term individual therapy, group therapy, or bibliotherapy plus short-term individual treatment. We also consider the negative effects of psychoanalysis on outcome.

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