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Bishop Museum

Built as a memorial to his wife by Charles R. Bishop the museum’s first hall was built in 1889-1890.
Editorial

Norman Goldstein MD
Editor, Hawaii Medical Journal

Report to the Hawaii Medical Association Annual Meeting

Our Journal was first published in September 1941. Harry L. Arnold, Jr., M.D. served as the first Editor – for 41 years. Following Harry were Doris R. Jasinski, M.D. and the late J.I. Frederick Reppun, M.D.

When Fred asked if I would take over as Editor in January 1994, he advised, nay warned, that it would be a lot of work. He was right! Despite the time involved, it has provided an opportunity to review many interesting, some unusual, and occasionally controversial manuscripts. With the help of our Peer Review Panel including more than 200 members of the Hawaii Medical Association, the Editor’s tasks are lightened significantly.

During the last twelve months were six Special Issues:
- A memorial to Thomas J. Whelan, Jr., M.D. (November 1999)
- Issues in Current Healthcare and Reports from the American College of Physicians and the American Society of Internal Medicine/Hawaii Chapter (February 2000)
- The long-awaited Journal on Pain (March 2000)
- A trilogy of issues from the Third Pacific Vascular Symposium on Venous Diseases (April, May and June 2000)

My sincere appreciation to News Editor Henry Yokoyama, M.D. and Russell Stodd, M.D., author of the “Weathervane”, for their excellent contributions. Keep them coming, Henry and Russ.

Thank also to Doctors Ann Catts, Drake Will, and Al Morris for their help with manuscript editing. Our advertising representative, Michael Roth, keeps us in the black; our Managing Editor, Becky Kendro, and Editorial Assistant, Drake Chinen, keep us on time. Cover artist Dietrich Varez keeps us looking good.

On to the next millennium.
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Complete spontaneous regression of cancer: Four case reports, review of literature, and discussion of possible mechanisms involved

Walter Y.M. Chang, MD, FACS

Abstract

Spontaneous regression or remission (SR) of cancers has been defined as the disappearance of the malignancies without any treatment or with obviously inadequate treatment. Four case reports are presented. These include a case of pleomorphic liposarcoma with bilateral lung metastases, a case of recurrent squamous cell carcinoma of the esophagus following esophagectomy a year earlier, a case of a squamous cell carcinoma of the scalp, and a case of a ruptured hepatocellular carcinoma with an emergency right hepatic lobectomy but with some gross cancer remaining in the left hepatic lobe.

The literature of SR of cancers was reviewed and various mechanisms possibly involved in the disappearance of the cancers were discussed. Although immune modulation has been stated to be the most likely process causing SR, other mechanisms, such as genetic therapy, withdrawal of carcinogens, infection, fever and vaccine roles, apoptosis, antibody, antiangiogenesis and maturation mechanisms, withdrawal of therapy, natural killer activity, endocrine, hormonal, and pregnancy factors, and prayers or psychoneuro-religious participation were also mentioned. Induction and inhibition of malignant protein expression and repair of gene damage may prove to be the more important processes in cancer regression.

It was also pointed out that the pulmonary metastases of the liposarcoma and the recurrent squamous cell carcinoma of the esophagus may be the very first cases of their kind to be described and that it is rare indeed to find 4 cases of SR's in a solo practice.

Finally, it is likely that SR is rarer than previously believed and that the incidence may be one in every 140,000 cases of cancer rather the one per 60,000 to 100,000 cancer cases as earlier thought.

Introduction

Spontaneous regression or remission (SR) of cancers has been defined by Everson and Cole as the complete or partial, permanent or temporary disappearance of all or at least a significant portion of a well diagnosed malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on the neoplastic disease. Remissions are supposed to last at least one month and should not just be the waxing and waning of stable disease. This definition of SR is considered unequivocal for cancer regression with no medical therapy, treatment failure, or therapy known to be failures.

The true incidence of SR is unknown, but Cole has estimated that probably it occurs in no more than once in 60,000 to 100,000 people with cancer. After a review of a large number of cases, Cole was able to document only 176 cases from 1900-1964. Lymphomas and leukemias were not counted. Therefore, if one SR occurs, on an average, in about 80,000 persons with cancer, it would require a single surgeon working about 30 years and seeing about 10,000 cases of cancer a year, before he would find 4 spontaneous regressions. But if only one SR occurs in 140,000 cancerous cases, a surgeon would need to see nearly 19,000 cases of cancer a year for 30 years, or a total of 570,000 cancer cases, before he would find 4 cases of SR.

Nearly two thirds to three fourths of all SR's occurred in just a few types of cancers. Furthermore, most soft tissue sarcomas occurred earlier this past century and have been difficult to find in recent literature. Even with the extensive review by Everson and Cole, only eleven cases of soft tissue sarcomas with SR were recorded. None were pleomorphic or dedifferentiated liposarcomas.

After a current check of more than 1200 citations and references in a literature search, it was hard to find any cases of regression of metastatic pleomorphic liposarcoma to the lungs and of recurrent squamous cell carcinoma of the esophagus. There was a case of spontaneous remission of lung metastases from an esophageal primary but the primary esophageal lesion did not regress except only partially. Furthermore, SR also seemed to occur much less frequently than previously thought and was found to occur at a rate of 1 per 140,000 cases of cancer.

Because of the extreme rarity of finding 4 cases of SR in a solo practice of a surgeon and because the patients with metastatic pleomorphic liposarcoma and recurrent esophageal squamous cell carcinoma may be the first cases of their kind to be reported, this paper is being presented with the 4 case reports, review of the literature, and a discussion of possible mechanisms involved in SR.

First Case Report

Mrs. A. T., 69-year-old part-Hawaiian and part-Caucasian woman, noted a 3.0 cm rounded, tender mass in the left gluteal area after a fall in late 1996. X-rays and sonograms showed a homogeneous soft tissue density, 5.0 x 5.2 cm, with well-defined margins in the left gluteal region suggestive of a hematoma. The lesion slowly increased in size and, therefore, surgical consultation was sought in December 1997. Except for the left gluteal mass, her physical examination was unremarkable.

MRI study of the left gluteal region showed an 8.0 cm soft tissue
mass involving the fat overlying the left gluteus maximus muscle without definite invasion of muscle. Excision biopsy of the lump was done on 01/09/98. With the exception of transient atrial fibrillation, she did well. The histological examination of the 12.0 cm x 7.0 cm lesion showed a high-grade pleomorphic liposarcoma. A surgical margin was focally involved. Subsequently, wide radical re-excision, including portions of the left gluteus maximus muscle, was carried out. Pathology examination revealed no evidence of residual sarcoma. She was seen in consultation by a medical oncologist and a radiation therapist. The latter subsequently delivered 6,480 rads to the left gluteal area.

Because of some necrosis involving the edges of incision, these areas were excised on 01/24/98. During the course of her therapy, studies revealed a lower left neck mass which required a left thyroid lobectomy on 02/25/98. Pathological examination noted an occult papillary carcinoma, 0.1 cm in greatest microscopic dimension without capsular or surgical margin involvement, associated with a multinodular goiter.

On 03/03/98, a large left hip seroma was drained by the insertion of two Jackson-Pratt drains. After the drains became plugged, the seroma reaccumulated, requiring frequent aspirations-drainage. Because of the persistent recurrence of the seroma, 250 mg of Doxycycline liquid was injected into the cavity in an attempt to sclerosate the area and allow adherence of the walls of the cavity. But this caused the injection site to become necrotic and an area 1.0 cm in size to blackened. An eschar developed at the site. Furthermore, the seroma persisted.

On 09/03/98, chest x-ray showed a 3.0 cm mass in the anterior segment of the upper lobe of the right lung, a 1.0 cm mass in the lower lobe of the left lung, and a 3.0 to 4.0 cm mass in the left hilum (Fig 1a). CT scan of the chest, on 09/10/98, confirmed the presence of these masses.

MRI studies of the left gluteal region on 09/16/98 showed only post-operative changes of the subcutaneous tissue. There was an encapsulated fluid collection or seroma in the operative site.

On 09/17/98, a CT guided needle biopsy of the left hilar mass was done. Pathological studies revealed malignant neoplasm, consistent with metastasis from the previously resected high-grade sarcoma of the left gluteal area (Fig 2a).

Before any new therapy could be given for the metastases to the lungs, another chest x-ray on 10/02/98 showed a decrease in the size of the pulmonary and left hilar metastases. Subsequent chest x-rays on 11/02/98 and 12/02/98 showed further regression of the lung and the hilar metastases. A CT scan of the chest on 05/14/99 and a chest...

Figure 1a. Chest x-ray shows metastases to lungs.

Figure 1b. Chest x-ray shows complete regression of metastases.
x-ray on 05/23/99 (Fig 1b) and on 08/02/99 revealed complete regression of all the metastases with no treatment at all.

On 08/11/99, excision of the left hip irradiated tissues, the eschar or necrotic injection site, and the pseudocapsule of the serous cavity were excised. Advancement of skin flaps were done for closure. Chest x-rays on 08/07/00 continued to show no evidence of metastases.

**Comment**
The evidence for spontaneous regression in this case is convincing. Histologically proven lung metastases disappeared with no therapy at all.

**Second Case Report**
Mr. M. S., a 57 year old Japanese man, had a near total gastrectomy, omentectomy, splenectomy, resection of the distal one third of the pancreas, jejunojejunostomy, and a feeding jejunostomy on 02/11/83 for a moderately well differentiated adenocarcinoma of the stomach superficially invading the underlying muscular layer. On 03/03/83, he had drainage of a left subphrenic abscess. Subsequently, he did well.

On 05/09/89, on a routine follow-up esophagogastroduodenoscopy, a 3.0 cm reddened area in the lower esophagus, 2.0 to 3.0 cm above the esophagogastric junction, was biopsied. The pathology report was squamous cell carcinoma of the lower esophagus. On 05/15/89, the patient underwent a resection of his gastric remnant and the distal third of his esophagus. An end-to-side esphagojejunostomy, side to side jejunojejunostomy and a feeding tube jejunostomy were also done.

Post-operatively, on 05/25/89, a gastrografin swallow showed a leak of the esphagojejunostomy site with communication to the left pleura space. On the same day, a tube was placed in the left chest to drain the empyema. During the placement of the chest tube, the patient aspirated some gastric contents and developed pneumonia. On 06/07/89, a tracheostomy was done. The chest tube was discontinued subsequently when the patient recovered. The final pathology report showed moderately well differentiated squamous cell carcinoma of the distal esophagus invading the submucosa but not involving the muscularis.

On 05/24/90, a year later, endoscopic biopsy of a 1.0 cm lesion at the esophagojejunal junction revealed recurrent squamous cell carcinoma. Five pathologists in three different hospitals in Honolulu, Hawaii, concurred that the patient had recurrent squamous cell carcinoma (Fig 2b). Consultants recommended further resection or radiation of the carcinomatous area. However, before any further therapy could be started, another endoscopy with biopsy done on 05/31/90 showed only severe inflammation. Repeated endoscopic biopsies done yearly from 1990 until 1998 did not reveal any recurrent squamous cell carcinoma. His last endoscopy and biopsy on 09/07/99 also showed no recurrent carcinoma and only a mild chronic inflammation of the esophagojejunal junction. He has remained free from his recurrent carcinoma without any treatment for at least 9 years.

**Comment**
Endoscopic biopsies were done a week apart in this case. The 05/24/90 biopsy showed recurrent squamous cell carcinoma while the 05/31/90 biopsy showed only inflammation. When subsequent endoscopies and biopsies showed no cancer, the original slides were reviewed and re-reviewed by three different pathologists at St. Francis hospital, by a Dr. H.N., from Queen’s Hospital who wrote a formal consultation confirming the recurrent cancer, and by a Dr. G.S. from Kuakini Hospital at a presentation during a tumor conference. All agreed that there was recurrent squamous cell carcinoma of the esophagus.

While regression in squamous cell carcinoma in the esophagus is unusual and this may be the first reported case of SR in a recurrent esophagus cancer, remission in a week would be rare, but there have been other cases of other cancers that have regressed rapidly. SR is, after all, a remarkable phenomenon. Why it should even occur is certainly unknown.

**Third Case Report**
Mrs. M. K., an 87-year-old Chinese woman was seen on 08/11/95 because of two large necrotic lesions on her forehead and scalp. The one on the forehead was ulcerated, 2.0 x 4.0 cm in diameter, and
umbilicated. On the vertex of the scalp was another similar 6.0 x 8.0 cm lesion that seemed infected. Past medical history revealed hypertension, end-stage renal disease, left ventricular hypertrophy, congestive heart failure, previous staphylococcus aureus sepsis, gastric ulcers, altered mental status, pancytopenia, and multiple thrombectomies of clotted Gore Tex grafts required for hemodialysis.

On 09/08/95, an excision of the 4.0-cm ulcerated lesion on the forehead was done. Undermining of the scalp with a rotation flap graft was performed to close the defect. Biopsies of the larger 8.0 cm lesion on the vertex of her scalp were taken. Both areas were diagnosed as squamous cell carcinomas of the scalp (Fig. 2c). She was seen by a radiotherapist for treatment of the larger squamous cell carcinoma involving the vertex of the scalp. However, because the patient was uncooperative, no radiation or further treatment was initiated.

On 01/29/96, about 5 months later, the scalp lesion started to disappear. The areas that were once ulcerated, necrotic, and crusted now seemed smoother although somewhat reddened. By early May 1996, the squamous cell lesions of the scalp had completely and spontaneously regressed without any treatment. The scalp now looked normal without any redness. She remained free of cancer without any treatment until 12/14/98, when at age 91 years, she expired from staphylococcus aureus sepsis.

**Comment**

Although no repeat biopsy was done during the three years of remission, the scalp of this patient, from early May, 1996, was completely normal to physical examination and to all observers. It would have been excessive to have done a biopsy to prove that the normal skin was normal. Besides, the family was reluctant to even bring the patient to the office for follow-up as there no longer was any abnormality on her scalp. It would have been very difficult to justify another biopsy since even an office visit was considered unnecessary by her family.

**Fourth Case Study**

Mr. J. C., a 53 year old Chinese man from Tahiti, was seen on 04/14/70 because of an enlarging mass in his right upper abdomen. Examination, at that time, suggested a hepatocellular carcinoma. His past medical history revealed a Billroth II gastrectomy for a large benign gastric ulcer and cirrhosis of the liver in August of 1966.

Just prior to his scheduled laparotomy, he became hypotensive and was rushed into surgery. A large ruptured hepatocellular carcinoma in the right lobe of his cirrhotic liver was uncovered. Hemoperitoneum was evident. The cancer extended into the medial segment of the left lobe of the liver. Because of the emergency nature of the operation, the hypotension, and the cirrhosis of the liver, only a rapid right hepatic lobectomy was done. Gross cancer was left in the left lobe of the liver. Recovery was fortunately rapid and the patient was discharged on 04/21/70, 7 days after surgery.

Subsequently, he was given 5-fluorouracil weekly for a month but, because the patient wanted to return to Tahiti, further chemotherapy was not given. He, however, survived for 21 years more without any known definitive therapy. The patient was last examined in May 1987, in Honolulu, at which time, he was found free of cancer. He survived 21 years and died on 02/02/91 in Tahiti with no evidence of recurrence of his hepatocellular carcinoma. The cause of his death was stated to be a stroke.

**Comment**

The pathological examination revealed the right lobe of the liver with a large ruptured hepatocellular carcinoma. The cancer had extended to and had involved the resected margin. Gross cancer was noted at the margins of resection on the specimen and on histological examination. At surgery, the cancer had invaded the left lobe of the liver. There were also nodules of cancer present in the left liver. Though cancer was left in the margin and elsewhere in the left lobe of the liver, this patient survived 21 more years without further treatment.

**Review of literature and discussion of possible mechanisms involved in spontaneous regression of cancer.**

**Incidence**

In a recent literature search for reports of complete spontaneous regressions of cancer, more than 1200 citations and references were secured. These involved papers from the 1970’s until the present. In addition, a large number of articles and books published before 1970 were also reviewed. The largest number of references involved instances of SR in leukemias and lymphomas.

Because of the inconsistency and variability of the SR’s in the leukemias and lymphomas, Everson and Cole chose not to include them in their description of the 176 cases of SR found between 1900 and 1964. Why leukemias and lymphomas display this inconsistent and variable behavior is unknown. Why they should form such a relatively large group so as to consist of more than 50% of the reports of SR is also unknown.

Besides the 176 cases found between 1900 and 1964 by Everson and Cole, another 188 cases of SR found between 1966 and 1985 were reported by Baker. However, Challis and Stam indicated that, between 1966 and 1987, there were 504 cases of SR. They included lymphomas and leukemias in their total.

A search of the literature for SR’s of cancer between 1986 and 2000 revealed another 139 new cases. Partial regressions or cases not well documented or histologically proven were not included. Lymphomas, leukemias, renal cell carcinomas, and melanomas again formed the majority or 67.6%. There were 43 cases of renal cell carcinoma and 18 cases of melanoma.

If these 139 cases were added to the 176 cases of Everson and Cole found between 1900 and 1964 and the 188 cases of Baker, found between 1966 and 1985, there would be a total of 503 cases of SR last century. But if the 504 cases of Challis and Stam were to be added to the 176 cases of Everson and Cole and to the 139 new cases, there would be 819 of SR’s of cancers during the past century instead.

Parkin has stated that the estimate of new cancer cases for the year 1990 for every country in the world was 8.1 million. This number, however, excluded non-melanoma skin cancers. One half of the total cancers occurred in developing countries.

During 1994, 1,208,000 new cases of cancer were diagnosed in the United States. In the mid 1990’s hepatocellular carcinoma, probably the most common cancer in the world was estimated to be
over 1,000,000 cases yearly, and all cancer in the United States
generally to be about 1,350,000 cases. In Grunlee’s article, there
was a forecast made of the number of cancer cases expected to be
diagnosed in the US in the year 2000. This number was 1,220,100.
Most will be lymphomas (62,300 cases) and leukemias (30,800
cases). Esophageal carcinomas will constitute 12,300 cases and soft
tissue malignancies 8,100.

Roughly, the number of cancer cases in the U.S. would be 19,500,000
in the period between 1985 and 2000. This would make an estimate
of about 1 case of SR for every 140,000 cases of cancer,

The next 3 cancers with frequent numbers of SR’s have been renal cell carcinomas,1,16,17,18 neuroblastomas,1,19,20,21,38 and malignant mela-
nomas.1,2,23,24,28 They form the largest group of solid cancers known
to have spontaneous regressions. Of the solid tumors, renal cell

Solid cancers with anecdotal cases of spontaneous regression
have also been described. Although of quite rare occurrences, lung
cancers,1,27,28,32,79,86 epidermoid cancer of the bronchus,78 hepatocel-
lular carcinomas,1,25,26,32 choriocarcinomas38 bladder malignancies,35 soft

tissue and bony sarcomas,3 prostate cancer,32 colon and rectal
cancers,3,32 malignancies of the ovary,32 breast,3,24,25 tests,39 uterus,1
bladder,32,34,37 stomach,3,32,37 larynx,1,37 thyroid,1,21 tongue,1

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Possible mechanisms involved in spontaneous remission

Documented reports of complete spontaneous remissions of cancers
are unusual, if not remarkable. Generally, regressions of cancers
have tended to occur in lymphomas, leukemias, kidney cancers,

Cytokines.5,6,9,81 especially interleukin, appear to play an important
part in tumor regression causing necrosis and apoptosis.57,65 The
latter effect can also be induced by cytokine proteases,38 thus leading
to spontaneous tumor regression in rat histiocytomas.

Immunological mechanisms:

Interleukin has been used effectively to inhibit cancer growth.3,85 SR
is thought to be the result of an efficient immune response against
melanoma cells in vivo critically influenced by a complex network
of interacting cytokines present.57,85 Viral infections inducing host
production of interferon with inhibition of tumor by interferon have
been thought to be mechanisms for SR.3 The normalization of
OKT4/OKT8 ratio may be a factor in cancer regression as suggested
by Ribera8 and Hansen.69

Chromosomal or genetic mechanisms:

Chromosomal or genetic abnormalities5,6,9,10,13,14,74,75,76,81 have been
evident in cancer for some time. There has been also some information
indicating that chromosomal manipulation such as deletion and
enzymatic blockage74 can cause remission.

DNA damaged by radiation or tobacco smoke can result in
mutations commonly found in human cancers, such as lung carcin-
omas. Spontaneous oxidation of guanine residues in DNA generates
8-oxoguanine (oxoG). By mispairing with adenine during replication,

What is also interesting is the observation that partial or complete
spontaneous regressions of the solid tumors, renal cell

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Abikinase in CML and has had quite impressive complete hematologic responses in Phase 1 studies.

**Gene switching**

One of the more recent, interesting researches involving regressions of cancers has involved the “switching off and on of cancer” in mice. By putting the antibiotic tetracycline in the drinking water of leukemia stricken mice, even advanced stages of the leukemia disappeared. But when the antibiotic-spiked water was withdrawn, the cancer returned.

The mechanisms apparently involved the 2 genes, Bcr and Abl. Fusion would occur in a process called chromosomal translocation whereby the 2 genes fused when they were out of their normal positions on chromosomes. Inside a cell, the fused genes Bcr-Abl would direct production of tyrosine kinase. This enzyme would promote a chaotic proliferation of white blood cells in the bone marrow thus resulting in leukemia.

Given the tetracycline, these mice would switch off the gene and its leukemia-producing activity. Cancer cells then would stop reproducing and would begin to die. Cancer reversal in some animals have been induced as much as three times.

Tetracycline in mice and tyrosine kinase inhibiting drugs in humans can inhibit leukemia generation but they do not eliminate the fused Bcr-Abl. If resistance to the inhibitor develops, either species will relapse with leukemia.93

**New Approaches**

New approaches which attack the molecular mechanisms by which the tumor gets its blood supply and hence its growth factors and oxygenation have been described.104 It is quite well known that the greater the amount of vascular endothelial growth factor (VEGF) present in a cancer, the more rapid the tumor growth. VEGF, produced by a gene isolated by Genentech’s Napoleone Ferrara, is critical for the production of blood vessels. Embryos with defective VEGF genes die before birth because of the failure to grow normal blood vessels, evidence for the role of VEGF as a key player.

Molecular biologists Peter Hirth and Gwen Fyfe of Sugen/Pharmacia Corporation have tried to deactivate the receptor sites of VEGF, whereas Genentech has designed a monoclonal antibody to VEGF that slowed tumor growth in animals by preventing VEGF from docking with its receptor. These antibodies are engineered versions of natural immune system fighters that attack a particular target. Clone systems, a New York company, has also entered the fray with a designed antibody against VEGF that it hopes will be more potent than that of Genentech’s. Novartis and Astra-Zeneca are also testing drugs to block VEGF.

This idea of starving tumors by antiangiogenesis has been attributed to Judah Folkman whose effort with Entremed in Rockville, Maryland, targeting angiostatin and endostatin seems less advanced than the VEGF research.

Still, VEGF blockers alone may be inadequate and, therefore, work on blocking mutant genes that avoid growth-inhibitions mechanisms and investigation on genes that may cause cell death or apoptosis are being done. Similarly, Genentech has genetically engineered Herceptin to repress HER 2 protein and to kill cancer cells.

Epidermal growth factor receptors (EGFR) is important for cancer growth.105 Abgenix Company has manufactured a monoclonal antibody against EGFR by injecting human EGFR into mice to create antibodies. But when the mice antibodies are injected into humans, the latter correctly identifies the mice antibodies as foreign and destroys them before they can fight the cancer.

Abgenix has been able to change and disable the mice genes that make the antibodies. Human genes are then inserted into the mice. These human genes direct the production of human antibodies. The result is the Xenomouse which still recognizes the human protein as foreign, but which responds by making human antibodies acceptable to the immune system of human patients.

Adenoviruses, used to introduce p53, a tumor suppressor gene, have been studied by Introgen Therapeutics. Many cancer cases are

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missing a p53 gene or have a defective p53 gene. By the introduction of a functional p53 gene, the cancer associated error in the DNA can be spotted and cell suicide or apoptosis can be triggered, thereby avoiding cancer spread.106

Withdrawal of Carcinogens
Elimination of carcinogens or irritants may play a role in the regression of cancers, especially if the lesion is still in the preinvasive stages.81 Some malignancies in the bronchial epithelium have regressed with cessation of smoking. Preinvasive changes in uterine cervical cancer, leukoplakia of the mouth, and carcinoma-in-situ of the bladder or colonic polyps have also undergone regression with removal of irritant factors.

Infection, fever, and vaccine mechanisms
One of the most prominent events mentioned in many cases has been fever or sepsis.88,89,90 Infections, fever, or even vaccinations associated with the cancer have wrought beneficial effects frequently associated with the disappearance of the cancer.5,14,15,30,42,79 Why this happens is unknown. In most articles, some influence on the immune system is mentioned as affecting the cancer.

Apoptosis, Antibody, Antiangiogenesis and Maturation
Reasons for SR whether through apoptosis,82 antibody formation,7 antibody antiangiogenesis,94 maturation of the undifferentiated cells,8 cytoxic or killing activity in the patient’s blood,31 activation of tumor necrosis factor86 have all been diligently studied. Studies have suggested that interleukin-4, a cytokine produced by mast cells and T lymphocytes, can cause growth inhibition in human breast cancer cells by inducing apoptosis.97 Programmed cell death (apoptosis) also has been correlated with an increase of a protein labeled BAX, whereas Bcl-2, another protein, has been shown to inhibit apoptosis. This can be exhibited by infecting human cancer cells with an adenovirus expressing the cancer growth suppressor gene, mda-87.98 Apoptosis in the prostate is activated by hormone ablation and is under the control of several regulating genes including the tumor suppressor gene p53 and the proto-oncogene bcl-2.99

Withdrawal of therapy
Bissods and Kaczmarek55 reported a case of SR of prostate cancer after withdrawal of diethylstilbestrol therapy. Since a significant proportion of lymphoproliferation disorders have regression of their disease after methotrexate therapy withdrawal, Salloum, et al106 have suggested that this fact may have important implications in the management of lymphomas.

Natural killer activity
So-called natural killer activity has been found in the blood of patients with lymphoma,51 renal cell cancer,18 neuroblastoma,19 and histocytoma.54 How this killing activity is initiated and the mechanisms through which it works have not yet been uncovered.

Endocrine factors and hormonal and pregnancy influences
That hormones can influence breast cancer is well known.31,34,47 The role of tamoxifen, lactation, pregnancy, estrogen, and cortisone in their influence on breast carcinomas are excellent examples of the endocrine effect.

Prayer in spontaneous regression of cancer
Recently, Harris,88 in a randomized, controlled trial, pointed out the positive outcomes in patients admitted to the coronary care units affected by remote intercessory progress. This appeared to be a confirmation of Bryd’s73 study on the beneficial effects of intercessory prayers again in a coronary care unit population. Hirschberg and Barasch [31], in their recent book, suggested that optimistic, positive attitudes and spirituality helped in cancer cures and possibly even with SR. It would be, of course, extremely difficult to prove conclusively a connection between prayers and SR.

In a study by Berlan,78 a large percentage of patients attributed their recovery to their prayers and to God.

In case one of this paper, the SR was attributed, by the patient, to the intercession of Father Damien.32 Her faith and belief in the benefits of prayer led her to write to the Pope in Rome and to start the process for the canonization or sainthood of Blessed Damien when her bilateral pulmonary liposarcoma metastases all disappeared.

In case two of this paper, the patient prayed to Buddha. According to Tseng70 and Chan,87 prayers allowed the “chi” or vital energy to flow unrestricted from the body and allowed the mutated cancer cells to mature or differentiate and revert back to a normal state. It is unknown whether prayers were used in cases 3 and 4 of this manuscript.

Of course, the most famous story of prayers affecting cancer is that of St. Peregrine, the patron saint of cancer.32 When the latter was a young priest, he was scheduled for an amputation because of a cancer of his leg. The night prior to his operation, he prayed fervently, dreamed that he was cured, and, on awaking, he was indeed cured. He was canonized St. Peregrine in 1726.

That prayers influenced the SR’s in cases 1 and 2 described in this manuscript can be difficult, if not impossible, to prove. Mention of the connection between SR’s and prayers is made as part of the discussion because of the fairly large number of writings in the review of the literature and for the completion’s sake.94

Comment
Why SR occurred in the above 4 reported cases is unknown. Could it be the infections or inflammation or necrosis in the first 3 cases? The 4th case of the ruptured hepatocellular carcinoma and cirrhosis of the liver with the emergency right hepatic lobectomy did not have sepsis.

In the case of the metastatic pleomorphic liposarcoma, doxycycline was injected into the left hip seroma cavity. Could it be that the doxycycline, an antibiotic synthetically derived from oxytetracycline, behave similarly as the tetracycline given to the leukemic mice in Huettner’s experiment,83 thereby cause a “switching off” of the liposarcoma proliferation? But the doxycycline was given 6 months before the metastases appeared.

It should be emphasized that the four cases of SR described in this article were well documented, well diagnosed, and histologically proven, and without any treatment or treated inadequately to exert a cure as in case 4 when only a emergency right hepatic lobectomy was done and gross cancer was left in the left lobe. Yet all cases
showed complete and permanent disappearance of all of the cancers. Thus, they easily met the criteria as set forth by Everson and Cole.4

The author also had a fifth case of a 93-year-old mother of an internist with painless obstructive jaundice due to a hard mass, presumed to be a cancer, in the head of the pancreas. Because of her age and her physical condition, only a bypass with a choledochojejunosomy–roux-en-y was done. She survived another 10 years. Unfortunately, no biopsy of the pancreas was done and thus, this case could not be included in this paper as an example of SR because of the lack of histological proof.

Finally, adherence to the title and thesis of this paper would suggest that the definition of complete spontaneous regression of cancer be modified to state that it is the disappearance of all of a well diagnosed malignancy in the absence of any treatment or in the presence of therapy considered inadequate to exert a significant influence on the neoplasm. Regressions should last at least one year.

Conclusion

Four cases of complete spontaneous regression of cancers, a review of the literature, and a discussion of various possible mechanisms involved in the disappearance of the malignancies were presented. The four very rare events of SR are interesting because of the sparsity of solid cancers with SR. The metastatic pleomorphic liposarcoma in the lungs and the recurrent squamous cell carcinoma of the esophagus may be the first case reports of their kind.

SR’s may be even rarer than previously believed and the incidence may be one per 140,000 cases of cancer rather than the one per 60,000 to 100,000 cancer cases as earlier thought.

Most SR’s have been associated with leukemias and lymphomas and, therefore, SR’s of solid cancers are rare. The immune system of the patients with SR’s may have been influenced in some way by one or more of the variously described mechanisms to enable the body to destroy the cancers. Genetic induction and suppression of cancers have recently been shown to play important roles in cancer.

Although immunological processes are stated in the literature to be the most likely cause for SR, recent work has shown that genetic mechanisms may be the more important processes as shown by studies on gene damage, abnormal protein expressions and the correction or inhibition of the offending protein.

Exact pathways have not yet been delineated but various theories have been described. The mystery of SR has not yet been solved but some secrets are beginning to be unlocked.

It may be that the pathway to cancer regressions, spontaneous or otherwise, lies not in the “angel’s crown which is Immunity,”11 but rather in our genes and in the inhibition, correction, and in the prevention of their abnormal expressions.

Finally the definition of complete spontaneous regression of cancer was modified to state that it is the disappearance of all of a well diagnosed malignancy in the absence of any treatment or in the presence of therapy considered inadequate to exert a significant influence of the neoplasm. Regressions should last at least one year.

References

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The Relationship Between Type of Antidepressant and Neurovegetative Symptoms in Adult Unipolar Nonpsychotic Depression: An Opinion Survey

Jonathan K. Shepherd PhD, Elaine M. Heiby PhD, Julie A. Holmes BA, Iqbal Ahmed MD, and Claire J. Jones

Abstract
The bi-directional nature of the neurovegetative symptoms of depression, as well as the differential response to antidepressant medications, underscore the existence of possible subtypes of this disorder. This study surveyed 56 physicians practicing psychiatry in Hawaii for opinions regarding the most effective antidepressant medication for the following symptoms: hypersomnia vs. insomnia, psychomotor agitation vs. retardation, and gain vs. loss of appetite or weight. Fluoxetine was found to be the drug of choice for weight and appetite gain, hypersomnia, and psychomotor retardation. Mirtazapine was viewed as most effective for weight and appetite loss. Trazodone was found most effective for insomnia and nefazodone for psychomotor agitation. It is concluded that subtyping of depression should be investigated at the symptom level and the generalizability of the effects of each specific compound should be tested.

The heterogeneous nature of depression has led to research designed to identify subtypes based on diagnostic criteria, physiological and biochemical markers, etiological evidence, and differences in response to treatment. Identifying differential responses to antidepressant medications has become an important approach to subtyping given the rapid increase in prescribing these drugs in recent years. While there have been surveys attempting to identify factors affecting physician choice of specific antidepressants, such as severity of depression and comorbidity with anxiety, little is known about the relation of choice and presence of particular depressive symptoms. The purpose of the present study is to explore subtypes in terms of prescribing habits for a subset of symptoms that differ markedly across cases of depression, the neurovegetative symptoms that can occur in a bi-directional manner (hypersomnia vs. insomnia, psychomotor agitation vs. retardation, and gain vs. loss of appetite or weight).

It is widely accepted that the major antidepressant groups differentially alter several serotonergic and noradrenergic neurotransmitter systems, directly and indirectly. These antidepressants include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and second generation compounds (SGCs; including selective serotonin reuptake inhibitors [SSRIs]). Given the potential differential effects of antidepressants, it follows that some medications would be relatively more effective with certain symptoms of depression, particularly the bi-directional ones involving either an increase or decrease in neurovegetative behaviors.

In a recent review, Mongeau et al. concluded that agents that are 5-HT or noradrenaline reuptake inhibitors are equally effective for treatment of depression, but this conclusion was based on research that did not measure drug effects upon particular depression symptoms. Research on the effects of different antidepressants upon atypical depression, whose definition includes the reversal of the usual pattern of bi-directional symptoms mentioned above, has been mixed, although one laboratory has found the MAOI phenelzine to be superior to the TCA imipramine.

Only a few studies have explored the effects of the newer generation of antidepressants upon bi-directional symptoms. Equivocal findings may be due to the following methodological limitations of these studies: (1) use of global improvement scores to evaluate treatment outcome, rather than measures of the effect of antidepressants upon each bi-directional symptom; (2) inclusion of only one drug within the type(s) under investigation, limiting generalizability to other compounds classified within the same type of antidepressant; (3) definitions of atypical depression that include not only neurovegetative behavior, but also premorbid personality characteristics such as rejection sensitivity; and (4) use of heterogeneous and global criteria to label atypical depression that can include any two of four symptoms, which obscures information on the precise bi-directional symptoms involved. For example, using the Columbia criteria a case of depression could be labeled atypical if weight gain and psychomotor retardation (severe fatigue, leaden paralysis) are present. It would be unknown in this case if sleep was increased, decreased, or unchanged.

Because little is known about specific antidepressant drug-symptom relations, the purpose of this study was to survey psychiatrists...
about their prescription habits and clinical opinion of the most effective drug for bi-directional symptoms of unipolar nonpsychotic depression among adults. If physicians report symptom-specific efficacy of particular antidepressants, these observations would justify animal model testing and the conduct of clinical trials designed to create specific drug-symptom profiles along the lines proposed by Stahl.4

Method

Subjects. Participants were 56 psychiatrists practicing in Hawaii. Their medical specialties were as follows: 37 (62%) general psychiatry, 2 (3%) child psychiatry, 1 (2%) rehabilitative medicine, and 16 (27%) multiple psychiatric specialties. The mean age was 51.20 years (SD = 10.79) and 45 (80%) were male and 12 (20%) female. The mean years since licensure was 21.23 (SD = 11.14). Ethnicity was 2 (3%) Pacific Islander, 1 (2%) Hawaiian-part Hawaiian, 39 (65%) Caucasian, 11 (18%) Asian, 1 (2%) mixed, and 3 (5%) other. Their employment settings included 20 (33%) private practice, 5 (8%) hospital, 1 (2%) community health center, 3 (5%) university, 3 (5%) other, and 25 (42%) multiple settings. Some participants failed to report part of the demographic information, so percentages do not add up to 100%.

Materials. A fourteen-item Opinion Survey on Use of Antidepressant Medications was developed by the present investigators. The Survey provided the respondents with the list of three MAOIs, seven TCAs, and 12 SGCs (including SSRIs) that appear in Table 1. Three items asked respondents to rate on a 5-point Likert scale the frequency of prescribing each type of antidepressant for adults presenting with unipolar nonpsychotic depression defined as major depressive disorder, dysthymia, or depressive disorder not otherwise specified. One open-ended item asked what drug is most frequently prescribed by the respondent. Eight open-ended items asked the respondent to indicate the most effective medication for the following symptoms of adult unipolar nonpsychotic depression: weight loss, appetite loss, weight gain, appetite gain, insomnia, hypersomnia, psychomotor agitation, and psychomotor retardation. Two items measured diagnostic and treatment progress procedures typically used. These could include unstructured or semi-structured interview and mental status examination, structured interview, clinical rating or behavioral checklist, self-report questionnaires, and other unspecified devices. The remaining items concerned demographic information.

Procedure. Surveys were mailed to 196 physicians with an addressed and stamped envelop. Physicians were those known by the Hawaii Medical Psychiatric Association to practice psychiatry in Hawaii. Fifty-six (29%) returned the Survey within approximately one month. Due to the anonymity of the survey, the differences between responders and nonresponders are unknown.

Results

Because the participants’ reported opinions may have been affected by the assessment devices they typically use, it is important to consider these findings. In terms of establishing a diagnosis for unipolar nonpsychotic depression, 31 (52%) reported using unstructured or semi-structured interview and mental status examination, 1 (2%) self-report measures, and 23 (38%) multiple devices. In terms of treatment progress, 30 (50%) reported using unstructured or semi-structured interview and mental status examination, 1 (2%) self-report measures, 1 (2%) other devices, and 22 (37%) multiple devices.

Participants’ mean ratings on a 5-point Likert scale (1 = not at all; 5 = always) of the frequency of prescribing the three types of antidepressants were 1.55 (SD = 0.60) for MAOIs, 3.79 (SD = 0.76) for SGCs, and 2.38 (SD = 0.68) for TCAs. Therefore, MAOIs were prescribed not at all to rarely, SGCs were prescribed sometimes to usually, and TCAs were prescribed rarely to sometimes. An ANOVA indicated that the means were significantly different (p<.001). Fisher’s post-hoc least significant difference tests indicated that each mean was significantly different from the other two means when considering the familywise error rate.

When asked what drug on Table 1 they most often prescribed, 51 (83%) respondents reported SGCs and 1 (2%) reported TCAs (imipramine). The remaining respondents indicated multiple types of drugs. Of the respondents reporting specific SGCs as most commonly prescribed, 34 (52%) indicated SSRI’s (sertraline, fluoxetine, and paroxetine). The number and percent of respondents reporting they most often prescribe other SGCs are as follows: 2 (3%) nefazodone, 1 (2%) trazodone, and 1 (2%) venlafaxine.

In order to test whether there is an association between antidepressant drugs and each bi-directional symptom, Chi-square analyses of expected versus obtained frequencies were conducted both for type of drug and for specific drugs. The results for each symptom are listed below and reported in Table 2. Percentages do not total to 100 due to listwise deletion of missing data.
Weight loss. For type of drug, 18 (30%) reported TCAs while 29 (48%) reported SGCS to be most effective (Chi-square = 73.62, df = 2, p < .001). Of the specific drugs indicated as most effective, most (18%) reported mirtazapine (Chi-square = 16.13, df = 4, p < .003).

Weight gain. For type of drug, 2 (3%) reported TCAs while 46 (77%) reported SGCS to be most effective (Chi-square = 63.72, df = 2, p < .001). Of the specific drugs, most (43%) reported fluoxetine as most effective (Chi-square = 61.31, df = 5, p < .001).

Appetite loss. For type of drug, 17 (28%) reported TCAs while 30 (50%) reported SGCS to be most effective (Chi-square = 69.99, df = 2, p < .001). Of the specific drugs, most (43%) reported fluoxetine as most effective (Chi-square = 65.25, df = 2, p < .001).

Appetite gain. For type of drug, 1 (2%) reported TCAs while 46 (77%) reported SGCS as most effective (Chi-square = 65.25, df = 2, p < .001). Of the specific drugs, most (48%) reported fluoxetine as most effective (Chi-square = 76.97, df = 4, p < .001).

Insomnia. For type of drug, 7 (12%) reported TCAs while 44 (73%) reported SGCS as most effective (Chi-square = 58.46, df = 2, p < .001). Of the specific drugs, most (33%) reported trazodone as most effective (Chi-square = 38.52, df = 5, p < .001).

Hypersomnia. For type of drug, 1 (2%) reported TCAs, 44 (73%) reported SGCS, and 4 (7%) reported MAOIs as most effective (Chi-square = 277.10, df = 3, p < .001). Of the specific drugs, most (40%) reported fluoxetine as most effective (Chi-square = 56.13, df = 5, p < .001).

Psychomotor retardation. For type of drug, 5 (8%) reported TCAs while 44 (73%) reported SGCS as most effective (Chi-square = 58.47, df = 2, p < .001). Of the specific drugs, most (38%) reported fluoxetine as most effective (Chi-square = 41.78, df = 4, p < .001).

Psychomotor agitation. For type of drug, 13 (22%) reported TCAs while 36 (60%) reported SGCS as most effective (Chi-square = 57.61, df = 2, p < .001). Of the specific drugs, most reported nefazodone (22%) as most effective (Chi-square = 26.39, df = 5, p < .001).

Discussion
The results of this survey must be viewed within the limitations of the naturalistic survey method employed. The participants were a convenience sample of physicians whose names were on the mailing list of the Hawaii Psychiatric Medical Association and were not randomly selected. The differences between responders and nonresponders to the survey are unknown due to the desire to maintain anonymity. The survey was developed for this investigation and is of unknown reliability and validity. We report aggregate opinion data only, rather than objective case-by-case treatment and symptom profiles and outcome measures, so our findings are subject to reporting biases. In addition, many of the survey questions obtained frequency data on drug-symptom relations rather than Likert-like independent ratings in order to keep the survey brief (ratings would have required an additional 176 questions). Finally, we did not assess a range of patient and physician factors that could affect prescribing habits, such as other depression symptoms, side effects, insurance, marketing factors, past response to other drugs, Axis II co-morbidity, medical condition, type of psychiatric practice (e.g. private or institutional), type of training (e.g., biological-psychotherapy focus), and years of experience.

We found that the most common type of antidepressant medication prescribed for unipolar nonpsychotic depression and for each specific bi-directional neurovegetative symptom was a SGC (especially SSRIs). This finding is consistent with prior investigations of prescribing habits reporting that SSRIs were chosen most frequently by psychiatrists for outpatient depression regardless of patients' age, sex, race, or payment source.7

Our most interesting findings concerned what particular SGC was associated with specific bi-directional symptoms. Of the 12 SGCS to consider, the participants reported specific neurovegetative symptom effects for the following four compounds: mirtazapine, fluoxetine, trazodone, and nefazodone (see Table 2 for drug-symptom associations).

It is noteworthy that fluoxetine was reported as being most effective for hypersomnia, weight and appetite gain, and psychomotor retardation as these symptoms constitute a partial description of atypical depression according to the Columbia criteria.8 Our findings are consistent with Nierenberg et al.'s call for the investigation of the effects of SGCS on atypical depression.11 However, the Columbia criterion requires only two of these symptoms to be present, indicating the importance of investigating the effects of antidepressants at the symptom level.

The prescribing habits of the psychiatrists participating in this study indicate that clinicians tend to tailor their choices of antidepressants at least partly based upon neurovegetative symptom profiles. The reported antidepressant of choice varied as a function of the direction of change in psychomotor activity, sleep, and appetite or weight. Therefore, our findings support a subtyping or symptom-treatment profiling approach to unipolar nonpsychotic depression.1,2,3,4

The basis of symptom profiling by our participants of course is unknown. One possible explanation is that the clinicians are selecting compounds based upon what is known about the agent's differential effects upon certain serotonergic and noradrenergic neurotransmitter systems. For example, none of the agents in Table 2 are considered to inhibit dopamine reuptake but they do differ in terms
of sedative activity, anticholinergic activity, inhibition of norepinephrine and serotonin reuptake, and blockade of serotoninergic and noradrenergic receptors. Another possibility for our findings is that clinicians have also had the opportunity to observe patterns of the therapeutic and side effects of different agents upon presenting neurovegetative symptoms and prescribe accordingly. This symptom profiling would be consistent with reports of similar therapeutic and side effects in the literature.4

The reported differential effects of antidepressant agents as a function of presenting symptoms is inconsistent with arguments that all drugs that inhibit 5-HT reuptake are equally effective.7 The results of this study suggest that there is a need for clinical guidelines for the choice of specific antidepressant medications based upon the particular presenting symptoms of unipolar nonpsychotic depression.3,4 The findings support the investigation of animal models of neurovegetative symptoms of depression as well as the implementation of clinical trials that evaluate the generalizability of the effects of each drug compound across type of agent and across type of depressive symptom.

Acknowledgements

This paper was completed by the co-authors following the death of Dr. Jon Shepherd on November 23, 1998. Dr. Shepherd developed the hypotheses and general methodology for the study. We would like to dedicate this article to Dr. Shepherd who was an assistant professor in the Department of Psychology at the University of Hawaii.

We would like to thank the Hawaii Medical Psychiatric Association for providing a list of physicians practicing psychiatry in Hawaii and the participants of this study. We would also like to thank Dr. Daniel Blaine for consultation on the statistical analyses and Barbara Haia for help with inputting the data.

References

A year ago, a STROKE left John Monteiro with barely enough strength to lift one arm. Let alone Danielle, his three-year-old daughter. THANKS in part to RESEARCH made possible by over $1.2 billion in support from the American Heart Association, today John holds Danielle with no effort at all. And he lifts the spirits of others as a VOLUNTEER with the American Heart Association's Stroke Outreach Program. John is proof that research SAVES LIVES. And to us, nothing could be worth more. For more information call 1-800-AHA-USA1.
Transplant symposium (Oct. 12-13)

One of the best bargains in recent years has been the symposium on Human Organ Transplantation sponsored by the Honolulu Medical Group Research Foundation. Form a nominal $15.00 registration fee we attended two morning sessions and an evening banquet for two at the Ilikai replete with cocktails.

As we turned into the HIC parking lot on Sunday morning, a stony-faced, not-to-bright lot attendant growled, "Park to your right ... show’s over there." With the World Series being telecast live, the attendant probably thought it must be some show for so many to come out, on a Sunday morning at that. A dapper Vic-Hay-Roe gave with the welcome spiel and introduced Dean Cutting who promptly relinquished the podium with the remark, "Nobody stayed away from TV this morning just to hear me talk," Program chairman Dick Blaisdell gave with a cheery "mahalo" and described Irvine Page as "the distinguished clinical scientist scholar, editor, and himself a phenomenon of our times." Irvine Page prefaced this talk, An Introduction to Organ Transplantation, with the confession. "I am by nature a nasty person and it took me 65 years to find me... what doctors say at cocktail parties and in public are two different things, so a little bit of controversy is a good thing." We soon discovered that one mark of a great speaker is that he can ramble and yet sound coherent and interesting. The following are excerpts from Dr. Page’s ramblings: "We ask, why did an amorphous group like the transplanters (referring to the heart transplanters)... Some are great and some are just plain lousy... What we need to ask is "What are the priorities we want in life? My quarrel with the transplant boys is that they have tried to ignore scientific procedures... Medical people have no way of expressing themselves... The AMA has no way of expressing itself because it is such a large organization: it has to be a consensus... Consensus is a good thing, but not always... The government, recognizing that consensus of the majority is a weakness, has moved in... We should have a National Academy of Medicine which can take its place with the National Academy of Science... You know scientists are just plain awful... they have to be awful to be good scientists... but they have managed to weld themselves together... Make no mistake about it. Government policy will determine what course medicine will take... There is creeping Federalism. The Supreme Court says, "There is no such thing as a government grant without government control." In the transplant field we are already seeing this..."

Dick Blaisdell introduced Robert Good from the University of Minnesota, who talked on Rejection Phenomena: Basic Immunologic Concepts. Dick described the rejection phenomenon as "some tissues have the 'Aloha Spirit' and accept while others do not and reject." Bob Good, a husking, droop-eyed, computer-brained lecturer with a booming voice, spat out a staccato of facts and information, too rapid for us lesser endowed to digest. He seemed to cram what must have been a seminar’s course into a half-hour lecture (he later apologized that he was a bit rushed). We did understand his introductory joke, though, so all was not lost. Bob said: "speaking after Irving Page with his relaxed manner reminds me of the Indian out on a desert 25 years ago who was sending out smoke signals when he saw the awesome atomic blast and said, 'Chee! I wish I had said that..." We also gathered a few pearls here and there such as "Cellular immunological deficiency shows a ten to twenty per cent increased incidence of cancer while humoral immunological deficiency results in leukemia. Every known carcinogen is immunosuppressive, and all tumors have immunosuppressive agents. The immunological mechanism has anticancer properties."

After the barrage, we staggered to the coffee and doughnut counter to restore our benumbed neurons. Thomas Starzl from University of Colorado was a slower-paced lecturer, more our speed. He complained, "Mother said never follow a banjo act, but she never said what to do when there were two banjo acts." Tom reviewed his experiences with his three kidney transplant series. Following his second series (1964 to 1966) of 42 cases, in which histocompatibility was the theme, he concluded that matching was not the answer. His present triple drug regimen (Prednisone, Imuran, and ALG or ALS) was started in June, 1966, and in this series, he has a 95 per cent renal survival rate with a five-year survival rate of 20 per cent or better rate even with non-related cadaver kidneys. The problem with liver and heart transplants, he pointed out, is that there is no mechanical support system available like the kidney like the kidney machine.

Following Tom Starzl’s intelligible lecture, "surgery of Organ Transplantation," moderator Dick Blaisdell (who would make an ideal official welcome for the Hawaii Visitors Bureau) ef fused: "Mahalo to the out-going speaker, and Aloha to the new speaker." We were proud of Arnold Sienssen, director of the Hemodialysis Center, who—if he was a little awed by the presence of world authorities on organ transplantation—did not show any indication of it, and gave an excellent resume of the current status of hemodialysis and renal transplantation in Hawaii which compares favorable with other large medical centers on the mainland. During the panel discussion that followed, Robert Good explained that "every kind of genetically determined immunological deficiency is related to malignancy." The ultimate use of immunology is to eliminate the first tumor cells, but immunological means is not for large tumors." He launched upon a protracted dissertation on IgA and IgM and the reasons why immunological means cannot be used for tumor therapy. When he finished, Dick Blaisdell said grimly, "Mahalo after that explanation." Dick Ando, who sat next to us, commented solo voice, "It must be pretty good... I don’t understand it..."

On Monday morning, we were welcomed by smiling Joe Oren. Dick Mamiya moderated and we were treated to Robert Good’s "Tissue Typing" (an intellectual barrage which was impressive and nonetheless incomprehensible). Noboru Oishi then reported on tissue antigens among ethnic groups in Hawaii (a joint project with Mitsuio Yokoyama et al of the Kuakini Medical Institute). Noboru’s report showed that Chinese apparently have less tissue antigens than other local racial groups.

Before starting his final lecture, "the Future of Organ Transplantation," Tom Starzl glanced towards Mitsuio Yokoyama in the audience and in a reverent tone described him as the world authority on IgG. (We are happy to report that under our close scrutiny, Mitsuio’s head only swelled a few centimeters, but there was that ridiculously happy grin passed on his face all day and for many days to come.) "Now, may we have the first slide please," George Nagao, who was the projectionist for the day, reported plaintively, "Dr. Starzl, you have the controls." Then we all were in trouble, he retorted, as he searched for the controls on the podium. The projectionist is the usual scapegoat in early morning slide lectures," he explained sympathetically. Poor George certainly had trouble enough for the fuse blow during the slide session.

Tom Starzl explained some of the technical difficulties encountered in liver and lung transplant and discussed graft rejections. We learned that technical errors from vascular anomalies account for many of the deaths in liver transplants, and that livers can be preserved for only one day. The same triple regimen of Imuran, prednisone, and ALG is used in liver transplants. Tom pointed out that here in Hawaii, all Caucasians would be potential recipients and all Hawaiians and Japanese will be potential donors, since these groups have little antigen.

Following the coffee break introduction, physician-lawyer and editor of Professional Liability Newsletter, David Rubsam of Berkeley, described "the many legal trols waiting under the medical bridges to trap the unwary in the future when organ transplants are commonplace." The first troll, he says is the definition of death. Under existing law, there is no codification of brain death (i.e., when the brain shows a flat EEG for 48 hours). Other trolls under future medial bridges include the matter of "informed consent" and the allocation of organ resources. A final troll is the problem of social issues such as overpopulation, pollution, etc., which could result from keeping men alive until they are 100 to 125 years old. David warned, "Perhaps we are reaching a time when we will be able to say that technological progress per se is not automatically good. Maybe
it’s going to prove out that we have to make some really difficult decisions in the area of the biological revolution which is now taking place and that there will have to be some law limiting this progress.

We attended the transplantation banquet at the Ilikai and managed to get within a stone’s throw from Irvine Page, but even with several fortifying drinks under our belts, we lacked the temerity to go up and talk to one of the great outspoken medical thinkers of our times. In characteristically relaxed and rambling fashion, Dr. Page discussed the ethical aspects of transplant and we managed some desultory notes: “Ethics is a nice thing to talk about... The Federal government even spent $150,000 for a symposium on medical ethics... the concept of just what is ethics is widely misunderstood... People too often think of medical ethics as a rule book of absolutes dealing with what is legal and what is illegal. It is not that at all... Ethics is manual of good behavior, like an Emily Post of medical behavior that enables a physician to get along with other physicians and his patients... Medical behavior has to watch itself—not to give in to contemporary behavior, or we’ll end up like rabbits (sic)... The transplantation of kidneys was handled according to regular scientific procedure; i.e., get evidence, marshal it, and then publish... This evidence was not presented in the case of Capetown... Anyone who abrogates this is doing injustice... This is true for cardiac transplantors and any others who do not follow this procedure. For example, with Andrew Ivy and Krebiozen, it took 13 years of legal entanglements to demonstrate that there was nothing... Yet presented 13 years later to a lay jury, they still found some evidence that it worked... Unfortunately, everyone is making medical decisions... There is also a question of priorities. Should children be kept from kwashiorkor? Should we spend $150,000 to keep a 55-year when you consider life as eternal... As Alvarez says about small strokes: ‘Death takes little nibbles out of you’... There is no such thing as an absolute value in arrogate our values to the Federal government, the AMA or anyone else... There is no crisis in medicine and we have a body of knowledge to keep clear...” (We were relieved to learn that the “medical ethics” we keep harping about is an unwritten code of behavior, and a rather nebulous one at that.)

Editors Note:
Henry Yokoyama has been writing “News and Notes” in the journal since 1964. At that time it was called “Notes and News.” I commented about his coverage of the organ transplantation symposium held in 1969 in last month’s editorial. Without his approval we reprint his report at this time.

Henry many thanks for your reports, your insights and your humor -- keep them coming for many more years.

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Our Deeds Determine Us, As Much As We Determine Our Deeds.

The passing of William Dang, Sr. M.D. marks a great loss to the medical profession and to the Hawaii Medical Association. A true gentleman, a wise and kind father with an extraordinary medical progeny, and a proud past president of Hawaii Medical Association, Bill was instrumental in bringing affordable medical liability insurance to Hawaii’s physicians during the insurance crisis of the 1970s. As costs skyrocketed and virtually all underwriters vacated Hawaii, Dr. Dang and HMA Executive Vice-president Jonathon Won, convinced a then new physicians mutual, Medical Insurance Exchange of California (MIEC), to come to our rescue. Since then, MIEC has grown into a very strong organization, protects about 1150 practicing physicians in Hawaii, supports the HMA in multiple areas, and has provided excellent malpractice protection with very competitive premium rates. For this alone, and many other reasons, we all owe Bill Dang. We benefit from his legacy and treasure his memory.

Too Many Clowns And Not Enough Circuses.
The United States Army recorded the incidence of hospitalized ocular injuries over a 10 year period ending in 1995. Because the personnel who sustain eye injuries frequently become unfit for military service, the economic cost can be enormous. The highest rate of injury was in 17 to 19 year olds, and males were twice as likely to become injured. The annual rate was 77 per 100,000, and the rate decreased by 38% over the 10 year period. Interestingly, the great majority of injuries were not related to weaponry nor war. 21% were caused by machinery or tools, 18% due to fights, 18% transport injuries, 11% sports or training, and a mere 7% due to weaponry or acts of war (90% of those were non-battle activities). The outcome of the collection of data suggests that appropriate preventive measures would be useful in decreasing the incidence of ocular trauma. Should the army go sailing on the OSHA?

Computers May Reduce Man’s Limbs To Push-Button digits.
Robotic surgery is here. The Food and Drug Administration has approved the da Vinci system for minimally invasive surgery, and it is now being marketed by Intuitive Surgery, Inc., of Mountain View, California. Through a one centimeter incision, the surgeon controls the robotic arms which are viewed on a 3-D video screen and controlled with joysticks and foot pedals equipped with sensors to manipulate the instruments. The FDA said the safety and effectiveness of the new device is about the same as laparoscopy. Going a step beyond, the device mimics the dexterity of human hands, and the fine movements such as suturing and dissection are easier than with laparoscopy. Currently under testing in several hospitals for cardiac surgery, the device is expected to be useful in a broad array of surgeries. Who knows? If silicon valley has its way, many surgical procedures may be programmed onto floppy discs, and the entire operation can be performed by computer.

You Never Really Learn To Swear Until You Learn To Drive.
To avoid sitting in traffic jams, more commuters are opting for bicycles. Bike riders like the exercise and environmental friendliness offered by two-wheelers, not to mention the ability to whip past stalled traffic. As a result, the number of people biking to work has grown more than 20% in the last five years, to 7 million, and some businesses are offering lockers, showers and other bike-friendly facilities. The down side is that many motorists are loath to get stuck behind slower-moving bicyclers, and clashes between the two are rising in number and violence. For people ages 25 to 64, cycle-related fatalities have risen almost 30% in the last five years. Drivers throw beer or soda cans, cut bikers off and have even hit bikers. The cyclists are not innocent. They often ride on sidewalks, go the wrong way on one way streets, ignore stop signs, or traffic control signals, and sometimes throw objects at motorists. Caught in the middle are the police who must referee the sniping and bickering. At the root of the problem is the increased number of motor vehicles and the frequent traffic jams so many hours of the day in busy cities like Honolulu. Be careful out there.


The World Health Organization estimates that over one million children under the age of 15 in sub-Saharan Africa are living with HIV/AIDS, and the vast majority probably contracted the virus while breast feeding from their mothers. In the 1970s public health advocates fought a heroic battle with infant-formula makers. They charged that marketing methods induced poor women to rely heavily on formulas and many women used contaminated water or diluted the formulas, causing a serious threat to the health of babies. They vigorously pushed breast feeding. Now, in the heat of the AIDS pandemic, experts are saying that evidence strongly suggests that infant formula should be aggressively promoted. Drugs can block the transmission of the virus, but obtaining the medicine and getting it to the infected mother in proper time is another obstacle.

Injustice Is Relatively Easy To Bear; What Stings Is Justice.
The question of why a doctor gets sued is one every physician should keep in mind. The number one protection against a malpractice suit is the doctor-patient relationship. It is an established truth that many times when the doctor has committed a negligent act, the patient will refuse to file a complaint because of a genuine affection and respect for the doctor. Moreover, patients understand that bad results can occur, and are willing to accept that, if the doctor takes the time to present the problem and explain the bad result. The second point is doctor arrogance. Malpractice attorneys are delighted when they encounter an arrogant physician (usually a surgeon, and usually male) at deposition, because they know the jury won’t like the doctor. Even if there is no negligence, defense attorneys are inclined to settle a case when they find it difficult to “humanize” the doctor. Another major concern in malpractice cases occurs when the doctor is caught in a lie, even if there is no negligence. This is called an incendiary device, and trial lawyers love them. Juries are not stupid, and do not like liars. And always remember to write your medical records as if a malpractice attorney were going to read them, because perhaps one will.

We Live And Learn, But Grow No Wiser.
The National Highway Traffic Safety Administration has advanced new air bag rules. The new regulations encompass testing and deployment of the advanced air bags, which employ better sensors and controls than older, sometimes dangerous bags. The new rules require manufacturers to test air bags on unrestrained dummies of small women and children ages 1, 3, and 6. The original crash tests were conducted on average-sized male dummies, which caused some serious injuries and sometimes even death to small human beings. The advanced air bags will be gradually implemented beginning in September 2003 and continuing through August 2006. Manufacturers must reduce risk by installing automatic switches or sensors that detect the size of occupants and deactivate bags or adjust the force of inflation accordingly.

Man (And Woman) Is So Constituted That No Matter What Color You Are Everyone Requires About The Same Amount Of Food.
Who said life was fair? A comfortable suburban 2200 sq. ft. house with four bedrooms and 2 1/2 baths in Jackson, Mississippi, is valued at $126,500. The same house in San Jose, California, is valued at $708,600, while in Honolulu it would be valued at $372,700 (if you can find one). A gallon of milk on Maui costs $4.39, while in San Antonio the cost is $2.28. Figure in other items such as foodstuffs, taxes, transportation, utilities, and cost of doing business, and one can see why living in our island paradise means accepting a reduction in discretionary income.

ADDENDA
★ 95% of food poisoning cases are never reported.
★ Nearly 50% of bank robberies take place on Friday. Week-end party?
★ Does the little mermaid wear an algebra?
Aloha and keep the faith —rtsl

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