SPONTANEOUS REGRESSION OF CANCER: THE METABOLIC TRIUMPH OF THE HOST?

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Although the existence of "spontaneous" regression of cancer remains a doubtful phenomenon to many physicians, it appears that as the years go by, more are willing to concede that the phenomenon truly exists. The explanation for the increase in credence probably is that many more cases have been reported with unquestioned diagnosis (supported by adequate biopsy confirmation) and with undisputable evidence that no significant therapy had been performed. At any rate, this author is firmly convinced that the phenomenon exists. Boyd,[1] who has probably devoted as much or more attention to the condition as anyone, remarks that to shut your eyes and refuse to believe in spontaneous regression of cancer is as absurd as the attitude of Pasteur and Lister's critics, who refused to see the evidence so plainly demonstrated to them. Also one of the world's greatest clinicians (Sir William Osler[2]) believed sufficiently in spontaneous regression to publish a paper that described the regression of metastases in two patients with carcinoma of the breast. The first patient had a radical mastectomy by Dr. W. Halstead in October 1897. The axillary nodes were involved; histological confirmation was obtained. Evidence of metastases developed a year later, with pain in the back and down the legs, a lump in the other breast, and a mass in the sternal area. She began to improve shortly thereafter until, when seen two years later by Osler, she was completely well and the sternal mass had disappeared. The second patient developed evidence of spinal cord or nerve involvement 18 months after mastectomy, with complete paralysis of the lower extremities. Shortly afterward she began to improve; she regained use of her extremities but retained some stiffness of the back that required the use of a cane.

I wish to emphasize that the term "spontaneous" is a misnomer, because there is obviously a cause of the regression, but it is not known, thus justifying the term idiopathic or biological. Evidence is accumulating to indicate that the causes of regression may be as numerous as the causes of cancer, and as the years go by the causative factors appear to be increasing.

It is difficult or impossible to estimate how commonly spontaneous regression occurs, but Bashford[3] has been quoted as saying that it occurs about once in 100,000 cases of cancer. Boyers[4] has estimated that it occurs approximately once in 80,000 cases. If the truth were known, the present author believes it occurs much more frequently than that. The basis for this statement is that during recent years it has become more difficult to find patients with cancer who have not been treated. Yet, this decrease in the percentage of untreated cancer patients does not appear to have decreased the incidence of regression. The number of acceptable cases found by Everson and myself[5] has increased during the last 15 years of our study (see TABLE 1), but, as stated in the legend, this is no index of frequency. It is quite possible that many of the patients we have treated successfully might have developed a period of regression at one time or other if no therapy had been given; it is impossible to determine how often this might have occurred in these cases treated by us.

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TABLE 1

THE DISTRIBUTION OF THE NUMBER OF CASES OF REGRESSION*

Five-Year Period	No. of Cases	Five-Year Period	No. of Cases
1900–04	1	1930–34	2
1905–09	3	1935–39	10
1910–14	2	1940–44	6
1915–19	3	1945–49	12
1920–24	3	1950–54	33
1925–29	5	1955–59	49
	1960–64	47	

* Taken from Everson & Cole.[5]

† An examination of number of cases reveals a much higher incidence for the last 15 years of this study, that is, 1950–1964. However, these figures are not valid, because there has been a much greater interest in spontaneous regression of cancer during recent decades than in the earlier ones.

Spontaneous regression may be defined as a partial or complete disappearance of a malignant tumor in the absence of treatment that ordinarily is considered capable of producing regression. The regression need not progress to complete disappearance of the tumor; obviously, the phenomenon is not synonymous with cure. In these cases,[5] some tumor masses regressed in one area, whereas in another area they remained unchanged or continued to grow. The patients with partial regression were included because it appeared that the factor that caused regression in that group was probably the same as in the group with complete regression, except for the duration. Therefore, if cases of temporary regression are excluded, much useful data that concerns the phenomenon of spontaneous regression might be lost.

COLLECTION OF CASES

In this monograph,[5] all the cases reported in the literature from 1960 to 1966 were included, in addition to cases referred to us by friends during this period (see TABLE 2). The leukemias, lymphomas, and squamous cell epitheliomas were excluded, because many examples of these lesions varied greatly in their rate of growth. We encountered several hundred cases in the literature that were claimed to be examples of spontaneous regression, but when the above examples and the cases in which histologic confirmation was inadequate or therapy was considered possibly to be adequate for cure were all excluded, we were left with only 176 cases.

A review of the case reports revealed that the regression in 21 cases persisted for less than 6 months, in 10 for 6–12 months, in 25 for 1–2 years, in 35 for 2–5 years, in 35 for 5–10 years, and in 22 for 10 years or more. In 28 cases, no mention was made about the duration of the regression.

Adenocarcinoma (Hypernephroma) of the Kidney (31 cases: 20 males, nine females, in two sex not stated). The age of the 20 males varied between 34 and 75, with an average of 56. The ages of the nine females varied between 45 and 70, with an average of 57.

Regression of presumptive pulmonary metastases occurred in 28 of the 31 collected cases (e.g., FIGURE 1). In 23 of these 28 cases, the pulmonary metastases

TABLE 2

COLLECTED CASES OF SPONTANEOUS REGRESSION OF CANCER*

Type or Location of Cancer	Number of Cases
Hypernephroma	31
Neuroblastoma	29
Malignant melanoma	19
Choriocarcinoma	19
Bladder	13
Soft-tissue sarcoma	11
Sarcoma of bone	8
Colon and rectum	7
Ovary	7
Testis	7
Breast	6
Metastatic cancer, primary unknown	4
Uterus	4
Stomach	4
Liver	2
Larynx	1
Lung	1
Pancrease	1
Thyroid	1
Tongue	1
Total	176

* Taken from Everson & Cole.[5]

were first noted *prior* to removal of the primary tumor by radical nephrectomy. In 22 of these 23 patients, the pulmonary lesion regressed spontaneously after nephrectomy. In the other patient, the presumptive pulmonary metastases regressed without nephrectomy; the diagnosis of the primary tumor was made at autopsy.

In 21 of the 23 patients in whom presumptive pulmonary metastases were noted before removal of the primary tumor, there was no therapy except the nephrectomy. In the two remaining cases, one patient had testosterone implanted subcutaneously (in addition to the nephrectomy); the other patient was given prednisone in small doses.

In two patients, an exploratory thoracotomy was performed; a few of the pulmonary lesions were excised, with confirmation of metastatic adenocarcinoma on histological examination. One of these patients died subsequently; the autopsy revealed only one remaining metastatic lesion in the lungs.

Of the 23 patients in whom presumptive pulmonary metastases were noted prior to nephrectomy, 17 were known to be alive at the time of the case report, although in some cases the follow-up period was brief. Of the 23 patients, six were known to have expired. Autopsies were performed on all six, with death attributed to metastatic disease in four; in a fifth, the diagnosis was made from the primary tumor (at autopsy); the sixth patient died from congestive heart failure approximately 19 months after nephrectomy.

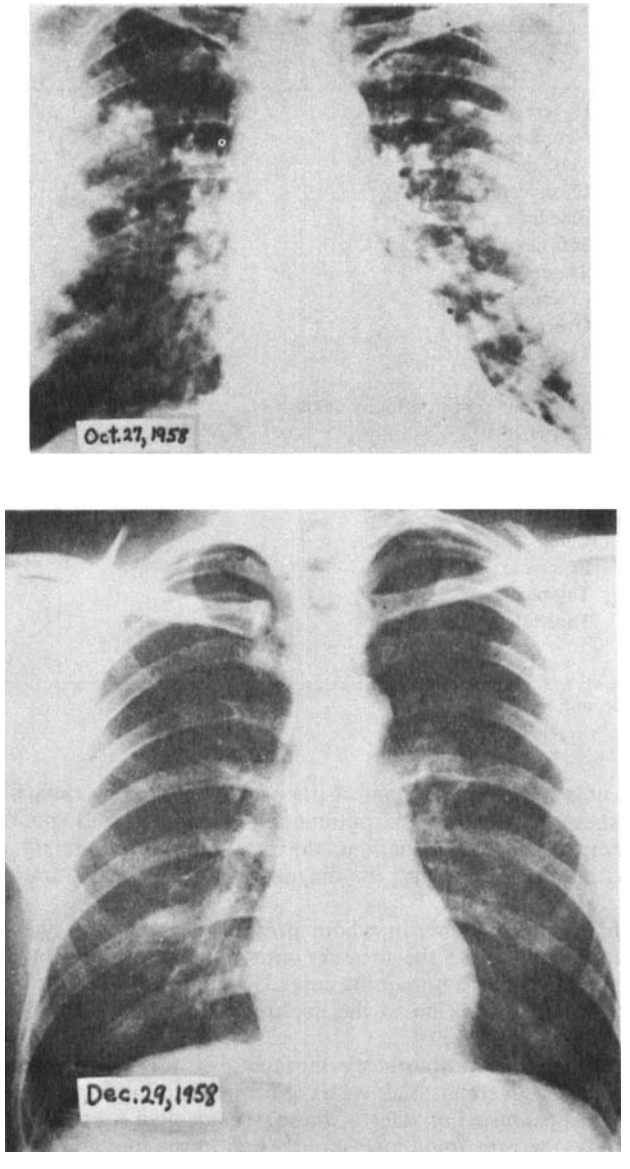

FIGURE 1. Sakula case of spindle cell carcinoma of the kidney, a male aged 61 years. (*Top*) Chest film October 21, 1958 reveals innumerable presumptive pulmonary metastases; (*bottom*) film 3 months later shows almost clear fields. Patient died a few months later. Besides the primary lesion, autopsy revealed only a few small metastatic nodules, all less than 0.5 cm. (From A. Sakula. 1963. By permission of *British Journal of Diseases of the Chest* 57: 147.)

Of the five patients who exhibited regression of the pulmonary lesion *after* removal of the primary tumor, all were alive at the time of the case report, although in some the follow-up time was brief. Of this group, four received no treatment; one patient received thalidomide, which has doubtful anticancer action. In one patient, examination of the surgical specimen indicated that the tumor was apparently not viable at the time of its removal. In another patient, gross and microscopic examination revealed almost complete calcification of the tumors.

One of the most dramatic of all these cases was a patient of Klimpel's,[6] who had a right nephrectomy on January 15, 1949 for a "typical Grawitz (hypernephroma)" in the midportion of the kidney. The patient demonstrated marked hirsutism of the body on the chest, lower abdomen, and back. After the wound had healed, x-ray therapy was given. On November 1, 1950 (almost 22 months after the nephrectomy), a piece of "coarse papillous tissue" the size of a plum and several smaller pieces of tissue were expelled during defecation after two previous brief episodes of intestinal hemorrhage. The patient retrieved the specimen and took it to his physician. On histologic examination of the tissue, which was partially necrotic but still easily recognizable, hypernephroid cancer was diagnosed. A barium examination revealed no abnormal findings.

On November 20, 1950, another plum-sized piece of tumor tissue was discharged (with slight bleeding) on defecation, again with histologic confirmation. On December 2, 1950, a tumor mass the size of a chestnut and several blood clots were expelled on defecation, again with diagnostic confirmation of malignancy. In May 1956, the patient returned with symptoms of pyloric obstruction, with x-ray confirmation. On July 3, 1956, 7.5 years after removal of the kidney, and 5.5 years after the last discharge of tumor tissue from the rectum, celiotomy was performed, with confirmation of obstruction by a benign ulcer scar. The abdominal cavity was completely free of metastatic disease. An anterior gastroenterostomy was performed with uneventful recovery.

Neuroblastoma (29 cases: 14 males, 10 females, in five sex not stated). In 21 cases, the presence of the tumor was first noted at less than 6 months of age, between 6 and 12 months in four cases, and between 12 and 24 months in four cases.

Neuroblastoma is the second most common intraabdominal tumor of infancy and childhood, being second to Wilms' tumor. In the majority of untreated patients, metastases develop rapidly and result in death within a few months. Because of this rather constant rapid growth of the tumor, a child who remains healthy for 12–14 months after treatment, with no demonstrable recurrence, may fairly safely be considered cured. Benson and associates[7] have stated that spontaneous regression has never been reported in a neuroblastoma that developed after the age of 2 years; this is also true of the present series.

In 12 of these patients, regression of the metastatic nodules or primary tumor occurred after biopsy of a subcutaneous nodule or metastatic lymph node. Of these 12 cases, five had a biopsy but no treatment, because the tumor masses were widely scattered over the body. Of the seven patients who received any therapy, one was given irradiation to the abdomen, without any evidence of regression; another received irradiation to the mediastinum. A third patient was given several courses of nitrogen mustard. Another was given arsenical drugs. The fifth received Coley's toxin. The final two patients were given prednisone, one of whom developed varicella, after which the subcutaneous nodules began to regress so rapidly that 4 weeks after the varicella most of the nodules had disappeared.

In seven additional patients, the primary tumor, or primary tumor and metastases, regressed after a biopsy of the primary tumor. One of these patients received Coley's toxin. A second patient was given triethylenemelamine for 3 days. Another received preoperative irradiation, without benefit. The four remaining patients were administered no treatment (except the biopsy).

Four patients had partial excision of the primary tumor, after which regression of the residual tumor occurred, without additional therapy. In two patients, complete excision of the primary tumor was performed after which the metastases regressed; one of these patients also was administered corticotropin, without discernible benefit.

In three patients, regression of liver metastases and the primary tumor occurred after a biopsy of the metastases in the liver. Two of these patients were given no other treatment. The third patient was given 1200 r preoperatively to the right kidney area.

Of the 29 collected cases, maturation of the neuroblastoma to a ganglioneuroma occurred in five. One of these patients received no treatment (except biopsy of the primary tumor). Two patients were given Coley's toxin. Another was administered nitrogen mustard, and the fifth received irradiation therapy to some subcutaneous nodules (see FIGURE 2). Cushing and Wolbach[8] were perhaps the

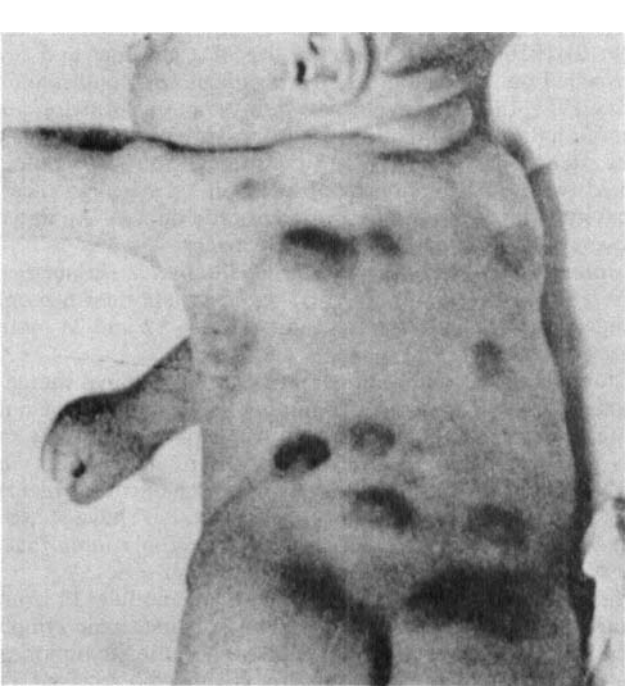

FIGURE 2. Vigorelly case of neuroblastoma in an infant 7 months of age. The photo was taken in July 1946. The numerous nodules have been covered with eosin to increase the contrast. Five irradiation treatments of 100 r each were given, followed by two additional treatments of 100 r 8 months later. *All nodules* regressed, the irradiated ones first. The patient is alive and healthy 16 years later. The original diagnosis was sympathicoblastoma; 5 years later a residual nodule was diagnosed as a ganglioneuroma. (From L. Vigorelly. 1962. By permission of *Minerva Pediatrica* **14**: 1219.)

first to report the transformation of a paravertebral sympathicoblastoma into a benign ganglioneuroma.

Although only 29 cases of spontaneous regression of neuroblastoma were encountered, it appears the incidence is much higher than that figure would indicate. For example, Koop and colleagues[9] noted that in a series of 44 cases with biopsy or partial removal of the tumor, a cure (spontaneous regression) was noted in seven (16%). Also, Dargeon[10] noted that of 25 patients who survived 5 or more years, 39% did not receive adequate therapy by irradiation or surgical excision.

Malignant Melanoma (19 cases: eight males, 10 females, in one sex not stated). The ages of the eight male patients ranged from 22 to 60 years, with an average of 41, and there was a range of 22 to 60 years for the females, with an average of 38.

Although malignant melanoma is not a very common tumor, it does constitute about 20% of all malignant tumors of the skin. Of the 19 cases in this series,[5] 17 were melanomas of the skin and two were primary tumors of the choroid. The primary tumor was excised or cauterized in all but one, in whom the primary tumor was never found.

In eight patients, regression of cutaneous metastatic lesions developed. In six of these, no treatment was given, except to the primary tumor. One patient was bitten by a rabid dog and was given 14 antirabies vaccine injections. Another patient received irradiation to some cutaneous metastatic nodules; surprisingly, some malignant cutaneous nodules that were not irradiated also regressed.

In six patients, the residual primary tumor or lymph node metastases exhibited regression. In four of these, no treatment, except the initial treatment of the primary tumor, was given. In one of these patients, a large abdominal wall tumor mass was excised. In another patient, an abscess developed in the region of the axillary metastases, which underwent regression.

In two patients, presumptive pulmonary metastases regressed. In two additional patients, presumptive pulmonary metastases regressed: one of these received no therapy, except for treatment of the primary tumor, whereas the other was administered antibodies tagged with ^{131}I. In another patient, subcutaneous lesions that were thought to be metastatic nodules regressed, and later the presumptive liver metastases regressed after the administration of 23 blood transfusions over a period of 4 months. During the last of these transfusions, he developed a tightness in his chest, and he displayed shortness of breath that so closely resembled a reaction to therapy that the transfusion was terminated. A few days later, the patient began to feel much better. Within 3 months, the liver edge was no longer palpable, and the urine was negative for melanin. For the next 4 years, the patient remained healthy. Plasma from this patient was given to another patient with pulmonary metastases from a malignant melanoma, but no improvement was sustained. In addition, plasma from the patient whose blood produced the incompatible manifestations was injected subcutaneously into a metastatic mass of malignant melanoma, without any beneficial benefit.

The blood of one of the eight patients (female, aged 30) described above, who displayed regression of cutaneous nodules without any therapy other than biopsy, had a remarkable curative effect when given to another patient with metastatic malignant melanoma. Four years after this patient demonstrated regression of her tumor, another patient (male, aged 28) with disseminated melanoma (head, right thigh, buttocks, and axillary lymph nodes) was given 250 cc of blood from the patient who exhibited regression. Within 6 weeks, the metastases described above in the second patient regressed completely; he remained free of any tumors

for 1 year, then developed a small metastasis in his finger, which was amputated. It may be significant that when a nodule 2.5 cm in diameter was removed from the supraclavicular region of the first patient, the mass ruptured and was removed piecemeal (possibly without removal of all the mass). Instead of developing a recurrent mass at the site of the biopsy, the wound healed and all evidence of metastases disappeared thereafter for 4 years, at which time 250 cc of her blood was given to the other patient with disseminated metastases, as described above, and with disappearance of all his metastases.

Choriocarcinoma (19 cases: 17 female, two male). The ages of the 17 female patients varied between 18 and 51, with an average of 28; the ages of the two male patients were 26 and 28.

Regression of presumptive pulmonary metastases occurred in 13 of the 17 female patients. In eight of these cases, the pulmonary shadows were first observed after the removal of the tumor by hysterectomy. In five of these eight patients, no other treatment was given, although one patient received irradiation therapy to the pelvis. Another patient who demonstrated regression of subcutaneous nodules was given 200 mg of testosterone, whereas a third patient was treated with chlortetracycline.

In three patients, the regression included primarily vaginal metastases. In one of these, vaginal metastases and pulmonary metastases were observed after hysterectomy, and the vaginal metastases disappeared after irradiation of the chest. In the second case, vaginal metastases were noted before the hysterectomy was performed; the regression occurred after this operation. In the third case, vaginal metastases were observed, but the regression preceded the hysterectomy.

In four patients, the pulmonary nodules were observed before treatment of the primary tumor, and they regressed after irradiation of the primary tumor or hysterectomy. Also, one of these four cases received prednisone, whereas another received antibiotics and corticoids.

In one patient, the primary tumor and vaginal metastases regressed after an attempted (but incomplete) resection of the primary tumor. In another patient, the pulmonary metastases that developed after irradiation of the primary tumor in the pelvis regressed after a second course of irradiation to the pelvis.

In one of the male patients, supraclavicular and presumptive pulmonary secondary metastases were first observed after removal of the right testicle, which contained the tumor; later, the right inguinal and paraaortic areas were irradiated. The pulmonary shadows and the supraclavicular nodules regressed 3 months later; the patient died 10 months later. In the other male patient, pulmonary shadows were noted before removal of the primary tumor by orchiectomy; they then disappeared but reappeared 6 or 7 months later, and he expired about 3 months afterward.

Two of the 17 female patients with spontaneous regression are known to have expired by the time the case reports were published. One of these died of probable metastases to the central nervous system about 2.5 months after regression of the presumptive pulmonary metastases; at the time of death, no pulmonary shadows had recurred. The other patient died with extensive pulmonary metastases after regression of a presumptive vaginal metastasis.

Cancer of the Bladder (13 cases: 12 male, sex not known in the other). The age of the 12 male patients varied between 49 and 69 years, with an average of 57.

The regression in 10 of the 13 cases occurred after the complete divergence of urine from the bladder by transplantation of the ureters into the colon or ileum preliminary to bladder resection. This would appear to offer good circumstantial

evidence that the urine contained a substance that was causing the tumor. Cystectomy was performed on nine of these 10 patients 21 days to 6 months after the ureteral transplantation. Examination of the surgical specimens showed no *gross evidence* of tumor. In four of these cases, there was no microscopic evidence of cancer, but in five there was. Cystectomy was not performed in one patient after transplantation of the ureters, but 4 months later regression of the tumor was noted on cystoscopy.

Regression of the bladder tumor occurred after transplantation of one ureter in two cases. In one of these two patients, the bladder resection and transplantation of the second ureter was performed simultaneously 8 months after the first transplantation; in the other case, the bladder resection and second ureteral transplantation was performed 9 weeks after the first transplantation. In both cases, gross regression was noted; in one patient, microscopic examination revealed no tumor, but residual cells were found in the other. The significance of elimination of the carcinogen will be discussed later.

Another patient demonstrated regression of liver metastases, although he developed a second cancer (colon). He underwent transurethral resection of a transitional cell carcinoma of the bladder in June 1955 (at 49 years of age), with frank microscopic invasion of the wall of the bladder. A barium enema (September 1960) revealed a filling defect in the lower sigmoid and an irregular pattern in adjacent segments of colon interpreted as diverticulitis. The patient suddenly developed an intestinal obstruction; he was hospitalized and a celiotomy was performed. Numerous nodules were found on both lobes of the liver; three were excised from the right lobe of the liver and two were removed from the left; microscopically, they were reported as metastatic carcinomas of the bladder. A large inflammatory mass was present in the pelvis. In view of the similarity of the roentgen deformity in the sigmoid to a diverticulitis, the lesion was considered benign; a colostomy was performed in the transverse colon to relieve the obstruction. During the next 3 or 4 months he gained 14 lbs, but he was administered another barium enema that revealed an obstructive lesion in the lower sigmoid colon. Operation was advised as a palliative measure in view of the liver metastases, but the patient refused. He was given cytoxin (200 mg/day) for 5 days. After a short period at home, he failed to deteriorate, so he consented to the operation, which was performed on May 4, 1961. The liver was palpated and *found to be completely free from metastases at this time.* An anterior resection with end-to-end anastomosis was performed. Microscopic section revealed adenocarcinoma of the colon. Convalescence was interrupted by an intestinal fistula and a large abscess that required resection of a bowel involved in the fistula; the liver was still free from metastases in January 1962. He was admitted to another hospital, in which some papillomata of the bladder were cauterized and radon seeds implanted into an area in the bladder where cancer was present. In January 1963, the patient was symptomatically well.

In this instance, the abscess could not be considered to be related to the regression, because this had predated the abscess. However, in the 5 or 6 years after the operation for an invasive tumor of the bladder, which was not completely resected, the patient developed another tumor (colon). Could this new tumor have resulted in regression of the liver metastases by causing the development of antibodies effective against the liver metastases? Possibly so, but it did not produce a cure of his primary bladder tumor, because he had an operation in January 1962, at which time a local recurrence of the bladder tumor was found.

Soft Tissue Sarcoma (11 cases: three male, eight female). The ages of the

three males were 17, 25, and 32, with an average of 25. The females varied in age from 5 months to 37 years, with an average of 14.8 years.

Regression occurred in four patients after incomplete removal of the tumor (see FIGURE 3). In one patient, the wound became infected postoperatively; in another, fever with a maximum of 102°F extended over a period of 5 days, although there was no evidence of a wound infection.

In four patients, the regression occurred after a biopsy of the tumor. One of these patients was given hot air baths postoperatively for a sciatic neuritis. Two of them had fever postoperatively: one, an infant, up to 38.8°C for 2 days, without evidence of wound infection; the other, a girl of 9 years, displayed fever of an unspecified amount for a few days postoperatively, with no evidence of wound infection.

One patient developed presumptive pulmonary metastases 1 year after amputation of the left lower extremity for an immature myxochondrosarcoma, but these shadows disappeared gradually 1 year later. Another patient underwent a resection of the right shoulder for a fibromyxosarcoma; 4 years later, large pulmonary metastases were discovered, but they remained unchanged for 5 years, at which time they became much smaller and calcified.

One patient with a hemangioendothelioblastoma of the jaw noted a sharp increase in growth of the tumor during pregnancy, but it decreased moderately after delivery. It was removed, but during pregnancy 2 years later it recurred; after delivery, it decreased in size and did not increase in size until she became pregnant a third time, at which itme it grew rapidly in size.

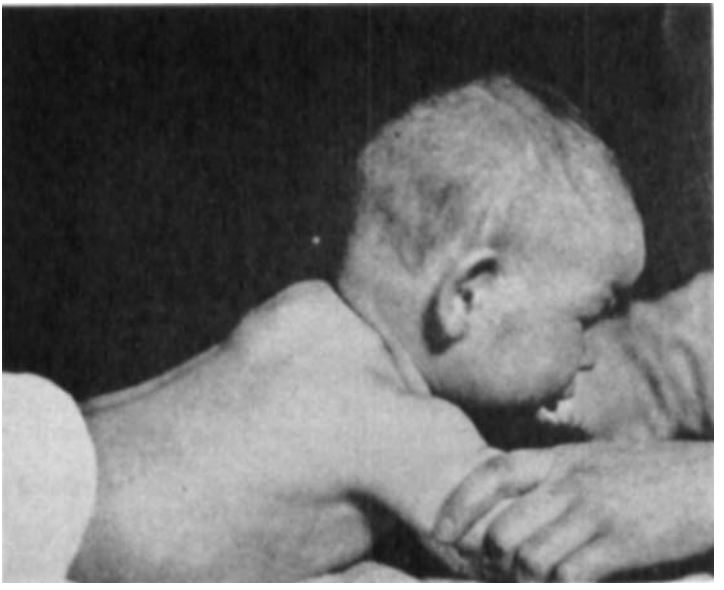

FIGURE 3. Shore case of fibrosarcoma in an infant 6 months of age. An attempt at removal of the lesion was unsuccessful because of the deep infiltration. Within 7 months, the mass began to regress; 1 year later no mass was noted. At the last examination 5 years after the operation, there was no evidence of tumor and the child was healthy. (From B. R. Shore. 1936. By permission of *American Journal of Cancer* 27: 736.)

Sarcoma of Bone (eight cases: four male, three female, in one patient age not stated). The age of the male patients varied between 5 and 27 years, with an average of 18; the age of the female patients varied between 12 and 29, with an average of 19 years. The diagnosis in four cases was osteogenic sarcoma (see FIGURE 4), Ewing's sarcoma in two, and reticulum sarcoma in two.

Regression of presumptive pulmonary metastases occurred in six patients. In five of these, the pulmonary shadows were first detected after definitive treatment of the primary tumor by irradiation or surgery. One patient demonstrated regression of the lesions in the left lung, but the masses in the right lung field increased in size until death. At autopsy, examination of the left lung revealed no gross or microscopic tumor, thus completely confirming the regression on x-ray. Another patient with a Ewing's sarcoma of the ileum and pubis (diagnosed by biopsy) had irradiation therapy, with a decrease in size but no disappearance of the masses. A large mass developed in the right lung 2 months later, but 9 months afterward the pulmonary mass had disappeared. Another patient had a mid-thigh amputation for an osteogenic sarcoma of the terminal end of the femur. Ten months after the amputation numerous dense shadows were observed over both lung fields. About 38 months later, these shadows were becoming smaller and calcified. Eighteen years after the operation, the nodules were still smaller and more deeply calcified. At this time, a thoracotomy was performed, and several of the nodules were removed; microscopic examination revealed only calcified scar tissue. Five years later, the nodules remained unchanged, and the patient was completely healthy.

In one patient who underwent an amputation of a lower extremity for a reticu-

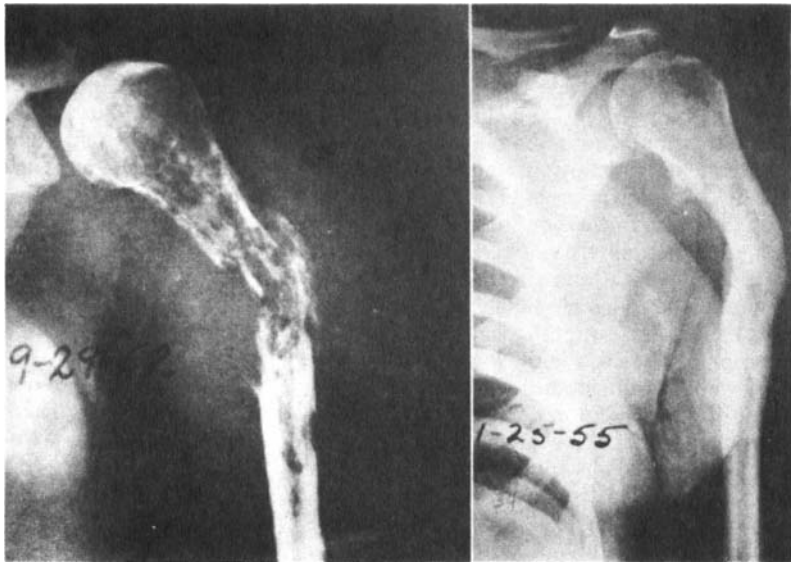

FIGURE 4. Levin case of an osteogenic sarcoma in a female aged 29. (*Left*) Roentgenogram reveals massive destruction with pathologic fracture; a biopsy confirmed the diagnosis, but malignant giant-cell tumor could not be excluded. (*Right*) Roentgenogram 3 years later shows complete healing. (From E. J. Levin. 1957. By permission of *Cancer* **10**: 377.)

lum cell sarcoma of the femur, local recurrence developed along the entire length of the remaining bone. This recurrence disappeared, however, after the administration of Coley's toxin. In another patient, the primary tumor diagnosed as osteogenic sarcoma of the humerus (with a possibility of malignant giant-cell tumor) disappeared after biopsy. In another patient with an osteogenic sarcoma of the femur, numerous presumptive pulmonary metastases were found on x-ray. Four months later, though, these nodules began to regress, and 2 months after this had completely disappeared. Shortly afterward, a fracture developed through the primary tumor; accordingly, a disarticulation at the hip was performed. Five years later,the patient was still healthy. She had been given vitamin B_{12} injections, both before and after the pulmonary lesions were noted.

Cancer of the Colon and Rectum (*seven cases*: *five male, two female*). The age of the male patients varied from 45 to 59 years, with an average of 50; the age of the female patients was 63 and 68 years. Four of the patients had cancer of the colon (two male, two female), and three had cancer of the rectum (three male).

Two of the patients had regression of the primary tumor and local extension, whereas two others had regression of local recurrences. One patient had regression of presumptive liver metastases, and one other had regression of multiple intraabdominal metastases and peritoneal implants, whereas another had regression of presumptive liver metastases. All seven patients were alive and healthy at the time of the case reports.

Two of the regressions were associated with abscesses. One of these patients was in good health until September 1950, when he developed an abscess in the left flank (with pain, fever, and loss of weight). A very foul discharge pervaded for 2 months, after which the sinus tract healed. However, the abscess recurred and was incised in March 1951; thereafter the sinus tract drainage persisted. The patient's weight declined from 170 to 130 lbs. In April 1951, an acute obstruction of the colon developed that required a colostomy. Abdominal examination at the time of the colostomy revealed a hard nodular, irregularly shaped mass, solidly fixed to the bony pelvis, and this tumor was considered inoperable. Culture of pus from the sinuses revealed only anaerobic streptococci. Microscopic examination of tissue obtained by curettage from the sinuses revealed an adenocarcinoma (grade II), which was probably of intestinal origin. Because of the hopeless fixation of the mass to the bony pelvis and confirmation of cancer by microscopic examination, no thought was given to resection; however, roentgen therapy (3000 r in 12 days) was administered. In September 1953 (2.5 years after the colostomy), he came to his physician with a request for closure of his colostomy. The sinuses had healed 1 month after he left the hospital in 1951. To the surprise of his physicians, the mass in the lower abdomen had disappeared and he was feeling entirely well. Barium studies revealed no colonic deformity, except for an unfilled segment of colon 6 cm in length at the site of the previous deformity. The mass disappeared after the roentgen therapy. Nevertheless, an operation was performed; no tumor was found, though. There was a colonic defect of 6 cm, as shown on x-ray, and also a defect in the colonic mesentery. The blind ends of the colon were excised and examined microscopically, but no tumor cells were found. Accordingly, a side-to-side colocolostomy was performed, and the transverse colostomy was closed 2 months later. Seven years later, however, the patient again developed a colonic obstruction, which at operation proved to be a carcinoma 7 cm below the site of excision and anastomosis for the former tumor. This second tumor was a mucus-producing adenocarcinoma, which was entirely

different from the former. This was another example of regression of tumor associated with an adjacent abscess.

Carcinoma of the Ovary (seven cases: the ages varied from 26 to 81, with an average of 54). Regression of peritoneal implants occurred in five of the seven patients. In two of these five, regression occurred after removal of both ovaries. In two patients, regression succeeded removal of the cancerous ovary only. In another patient, regression of the peritoneal implants occurred after a celiotomy, at which time a biopsy of the abdominal metastases was performed. Regression of presumptive liver metastases occurred after bilateral ovariectomy in one patient. In another patient, regression of the primary tumor occurred without removal of the ovaries. This patient finally died 14 years after the abdominal operation, with extensive retroperitoneal and pulmonary metastases.

Three of the five patients who displayed regression of the peritoneal implants were known to be alive and healthy at the time of the case reports. One of the two remaining patients who had died succumbed to adenocarcinoma of the left adrenal gland 20 years after the operation for cancer of the ovary; the other patient died from cancer of the ovary. Autopsies in both these cases failed, however, to reveal any recurrence of the peritoneal metastases that had disappeared.

Cancer of the Testis (seven cases: the age of the patients varied between 16 and 41, with an average of 30). In three cases, the tumor was classified as a malignant teratoma, in three other cases, as an embryonal carcinoma, and in the remaining patient, as a round-cell carcinoma. In all seven cases, the regression affected presumptive pulmonary metastases.

In three patients, the regression developed *before* removal of the primary tumor. In one of these, the pulmonary lesions regressed before removal of the primary tumor; in the other two patients, regression developed after removal of the primary tumor.

In four of the seven patients, the pulmonary shadows were first noted *after* removal of the primary malignancy (see FIGURE 5). In two of the cases (one with a large round-cell carcinoma, the other with an embryonal carcinoma), the pulmonary shadows disappeared after irradiation of the abdomen. In one of these two patients, the other testicle was removed.

Five of the seven patients were known to be alive and well at the time of the case reports, whereas the remaining two had died of generalized metastases.

Cancer of the Breast (six cases: all female). The ages of the patients varied between 37 and 65 years, with an average of 48.

In three patients, the tumor recurred after mastectomy, or mastectomy and irradiation therapy, and then regressed without definitive therapy. In one of these three cases, the regression involved the lungs, pleural cavity, and both axilla; in another, it involved the neck, breast, and liver; and in the third case, the lungs and liver were affected. Two of the three were alive at the time of the case reports; the other patient died of an asthmatic attack several weeks after the regression had been noted.

In a fourth patient, presumptive pulmonary metastases disappeared a few months after bilateral mastectomy, but were found on a chest film taken 9 months later.

In the fifth case, presumptive pulmonary metastases regressed at the time of menopause. In the final patient, pleural metastases developed 7 years after preoperative irradiation but shortly thereafter disappeared. This patient died of generalized metastases 2 years later. Autopsy revealed metastases in the ovaries but confirmed the complete regression of the pleural metastases.

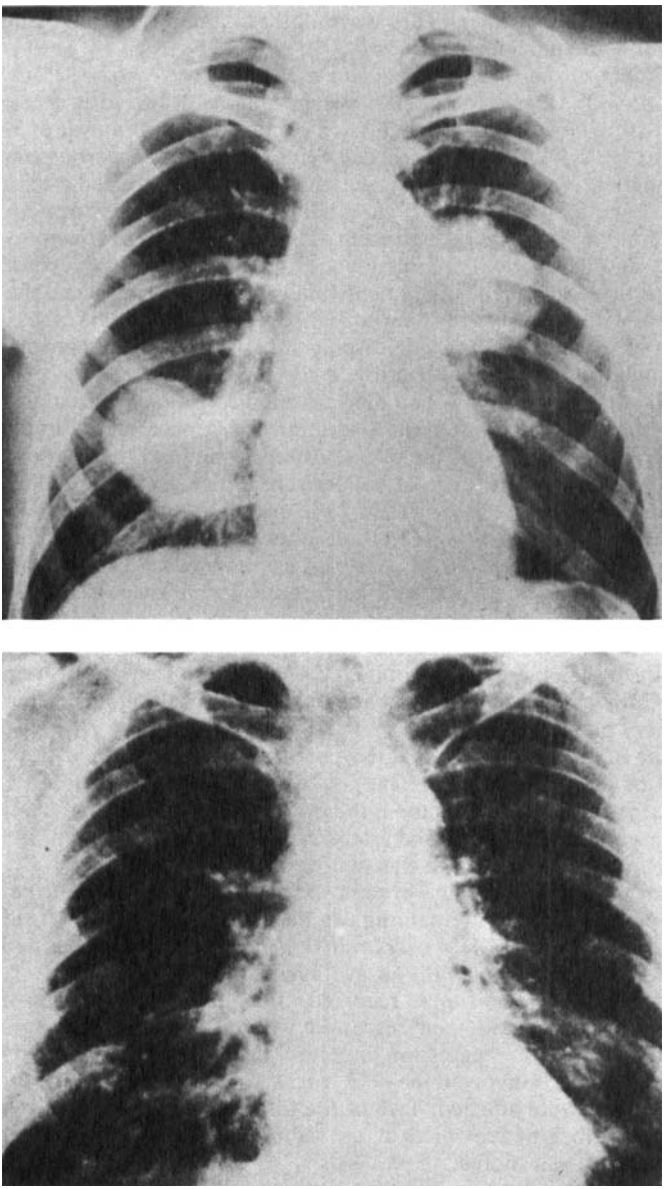

FIGURE 5. Boyd and Watson case of a teratoma, of the right testicle in a male aged 35. A right orchiectomy was performed April 7, 1954. Twelve days later, he underwent a paraaortic resection, which included several positive nodes; he was given postoperative irradiation to this area. (*Top*) Chest film taken March 15, 1955 reveals large bilateral presumptive metastases; (*bottom*) film taken 18 months later reveals almost complete regression of these masses. Another chest film 3 years later was negative, and the patient was free from symptoms. (Courtesy of T. A. Watson for *The Ontario Cancer Foundation.*)

Cancer of the Uterus (four cases). The ages of three of these patients were 33, 61, and 67; the age of the fourth case was not given. The tumor was classified as adenocarcinoma in two cases, as squamous cell tumor in one, and in one the tumor was not classified.

One of these patients had an inoperable adenocarcinoma of the uterus, which was confirmed by exploratory celiotomy. Three years later, after some improvement, she consulted another physician who performed a vaginal operation thought to be a hysterectomy and bilateral salpingo-oophorectomy. At examination 8 months later she had many hard nodular masses in the pelvis and a large fungating mass that filled the vagina. She improved considerably during the next several months, but died 3 years after her vaginal operation. At autopsy, the peritoneum was studded with calcified nodules up to 2 cm in diameter, but the vaginal mass was gone. The nodular masses could be examined microscopically only after decalcification; the malignant cells could barely be identified because of the fibrosis and calcification. Regression of uterine cancer does occur after castration but rarely to the point of the severe calcification that developed in this instance. Another patient expired of a presumed cerebrovascular accident 3 years after regression of numerous abdominal metastases that occurred after removal of the primary tumor by hysterectomy, but no autopsy was obtained.

In another patient, a primary squamous cell carcinoma disappeared more than 1 year after irradiation therapy, which had apparently provided no beneficial effect. Another patient had a recurrent tumor in the vaginal scar excised; microscopic examination revealed a carcinoma. This recurred and a recto-vesical-vaginal fistula developed. When seen a little more than 1 year later, the patient was healthy and the fistula had healed.

Cancer of the Stomach (four cases: three females, in one case sex and age not stated). The ages of the three females were 56, 58, and 60. The microscopic diagnosis was medullary carcinoma in one patient, adenocarcinoma in two patients, and in one patient the tumor was diagnosed only as a carcinoma.

The primary tumor regressed in three patients after celiotomy and gastroenterostomy. In two of these patients, the abdominal tumor masses disappeared; they were alive and well 10 and 11 years, respectively, after the operation. An abdominal operation was performed on the third patient 4 years after the clinical disappearance of the abdominal tumor mass; this operation revealed no gross or microscopic evidence of cancer.

In one patient, excision of the primary tumor by subtotal gastrectomy resulted in regression of the residual tumor that involved the transverse mesocolon and transverse colon. This patient survived an additional 16 years without manifestations of residual tumor and died of bronchopneumonia and hypertension; autopsy revealed no gross or microscopic evidence of cancer.

Miscellaneous Cases. There were two cases of regression of cancer of the *liver.* One of these was a 5-month-old male infant with a hard large liver that extended into the pelvis. At operation, a biopsy was obtained that was diagnosed as a malignant epithelial tumor of undetermined origin. Within 3 years, the child was healthy, and the liver had returned to normal size. The second patient with a regression of a liver tumor was a man 57 years of age who presented with an enlarged nodular anterior inferior portion of the right lobe. At operation, massive replacement of the inferior portion of both lobes was found along with numerous positive regional lymph nodes. Microscopically, the tumor was identified as a bile duct carcinoma of the liver. The patient was discharged untreated, but readmitted 3.5 years later with confusion, vomiting, dizziness, and other manifestations of

brain involvement; he died a few days later. Autopsy revealed a huge metastasis in the left cerebellum; the microscopic section displayed a tumor very similar to the original liver tumor. However, the left lobe of the liver was almost totally replaced by firm pale scar tissues, with no microscopic trace of tumor cells. The tumor in the right lobe was viable and possessed the usual malignant characteristics, except for one scarred area similar to that in the left lobe.

Another patient had a regression of a squamous carcinoma of the *larynx*, which was confirmed by biopsy. The patient refused all surgical or irradiation therapy. He was examined 4 years later and found to be well and with an apparently normal larynx. The same was true 8 and 12 years later.

A third patient had a regression of an inoperable squamous cell carcinoma of the right *lung*. At operation, the mediastinum and right hilum were involved. Frequent roentgenograms of the chest revealed progressive decrease in size of the malignant shadow. Five years later, he exhibited no manifestations of the tumor, and the chest x-ray was nearly normal. The patient had been employed as a linotype operator with exposure to noxious fumes. After the operation, he was prescribed two halibut liver capsules and four vegetable compound tablets that contained asparagus, parsley, watercress, and broccoli) daily.

Another patient (a nun) had regression of a cancer of the *pancreas*. The patient had been jaundiced for months. At exploratory celiotomy, the head of the pancreas was enlarged three times normal. A biopsy was obtained; a diagnosis of carcinoma was confirmed by three pathologists. The sisters of the order interceded in her behalf with prayer, and so on. She recovered rapidly from the operation and her very weakened condition; she returned to work for 7.5 years and died suddenly. Autopsy revealed a massive pulmonary embolism, but positively no evidence of tumor.

Analysis and Summary of Factors Encounted in this Series

After analyzing all the incidents or factors that occurred in the 176 cases in our survey, I find that they may be classified in roughly seven different groups, each of which contains several possible factors (see TABLE 3). Although any one or all of these innumerable factors might exert a role in spontaneous regression, I have no proof that any of them are truly the cause; they may have been entirely coincidental. The present author truly believes, though, that many of these factors exerted a definite role. Because each type of cancer is quite different from each other, it appears probable that there are many different causes of spontaneous regression. It does seem that if one knew the true causes of spontaneous regression, one would probably be able to identify the cause of many or most cancers.

In TABLE 3, the immunologic factors are listed first, largely because this author believes they are the most important, and similarly they are the most common of the factors encountered. Also, it is conceivable and probable that many of the other six possible causes listed actually were responsible for triggering an immunologic response of sufficient intensity to cause regression.

Many immunologists have stated that an immunologic response occurs frequently in patients with cancer but is so weak that if a large mass of tumor is present there is only a slight chance that it will be sufficient enough to destroy all of the tumor. For example, when speaking of the comparative destructive power of various therapeutic agents, Klein[11] stated that immune forces "can deal only with a certain maximum number of tumor cells as a rule." The fact

that 41 or more cases in our series regressed after excision of the primary supports this hypothesis.

Although a large number of the *metastatic* nodules in our series that were observed to regress had biopsy confirmation of a malignancy, it must be admitted that the vast majority did *not* have biopsy confirmation, although the primary tumor did. This is particularly true of pulmonary lesions; for this reason, we identified most of these (especially those in the lung, where biopsy would not be practical) as presumptive metastatic lesions. Autopsies were performed on many of the patients. Because many autopsies revealed malignant cells in masses that had exhibited marked regression in size, the supposition that the masses were true metastases is supported. The presence of such a large number of possible causative factors indicates quite clearly that there is no common denominator of possible factors.

Immunological Factors

One of the most intriguing of the possible immunologic factors is that encountered in the regression that occurs after transfusion (three cases of malignant melanoma). In one patient, the regression appeared after a transfusion of blood from a patient who had previously sustained a spontaneous regression from a melanoma; in another, the regression succeeded a transfusion from a patient who represented a 10-year cure after radical excision of a melanoma; the regression in a third case was seen after three transfusions from the blood bank, the last of which was blood group A, was Rh-negative, and produced a mild reaction. The regression in one patient occurred after administration of antibodies tagged with ^{131}I, in another after antirabies inoculations, and in a third after hot air "baths" for sciatica. Regression followed administration of Coley's toxin to two patients with soft tissue sarcoma, four patients with a neuroblastoma, and one patient with a bone sarcoma. Many of the regressions in the irradiation group (16 or more cases) could be explained more adequately by an immunologic rather than any other factor, because the vast majority of these were found in masses distant from the area irradiated or in masses irradiated one or more years previously. Similarly, the regressions in the four patients in the infection group appeared to be related to immunologic factors.

Reference has already been made to the 41 examples of regression after *excision of the primary lesion* and to the implication that eradication of the bulky primary tumor may allow the patient's immunologic mechanisms to be effective enough to destroy the metastases. This would not apply to the six melanoma cases, because these primaries were small. The tumor most affected by removal of the primary lesion was adenocarcinoma of the kidney; 22 patients in this group had regression of the presumptive pulmonary metastases after nephrectomy. Seventeen of these 22 were alive at the time the cases were reported. In five other patients, the pulmonary metastases were noted *after* nephrectomy.

In another group of 33 patients, regression succeeded a lesser type of operation (23 biopsy, 10 partial excision). This group of patients who demonstrated regression of their tumor without removal of the primary lesion might appear to be in contrast to the experimental data (mostly in rats) that revealed a decrease in resistance to a tumor after an operation. In our experiments,[12] however, the operation was a celiotomy with manipulation of the intestine for 20 min; we found that a lesser operation, such as incision through the skin, did not produce a decreased resistance to tumor.

TABLE 3

POSSIBLE CAUSATIVE FACTORS IN 176 CASES*

Immunologic	
After antibodies tagged with ^{131}I	1 melanoma
After blood transfusion:	
Regression of subcutaneous nodules after transfusion	1 melanoma
Regression after transfusion from patient with regression	1 melanoma
Regression after transfusion from patient with 10-year sarcoma	1 melanoma
After 14 antirabies inoculations	1 melanoma
After hot air "baths" for sciatica	1 melanoma, 1 sarcoma
After Coley's toxin	4 neuroblastomas, 2 sarcomas, 1 bone sarcoma
Hormonal	
After testosterone implanted subcutaneously	1 adenocarcinoma kidney
After 200 mg testosterone	1 choriocarcinoma
After prednisone	1 adenocarcinoma kidney, 2 neuroblastomas
After progestational agent	3 adenocarcinoma kidney
After delivery of child	1 sarcoma, 3 melanomas
During a period of amenorrhea	1 sarcoma
After excision of cancerous ovary	2 adenocarcinomas ovary
After excision of both ovaries	3 adenocarcinomas ovary
After celiotomy: biopsy of abdominal mass	1 adenocarcinoma ovary
After menopause	1 breast cancer
Trauma	
After excision of primary	22 kidney, 5 choriocarcinomas, 6 melanomas, 1 stomach, 2 sarcomas, 2 testicular, 1 breast, 2 uterine
After biopsy	1 liver, 12 neuroblastomas, 1 bone sarcoma, 1 adenocarcinoma kidney, 1 lung, 1 larynx, 1 pancreas, 4 sarcomas

Hormonal Factors

Because regression of tumors is frequently produced by numerous types of hormone therapy, it would appear that hormonal influence would be a common cause of spontaneous regression. In cancer of the breast, this hormonal influence is quite complex and at times contradictory. In young women (premenopause), advanced cancer of the breast will regress (for 3 to 9 months) after ovariectomy in 25–30% of cases. It almost always recurs, though, but it usually will regress again under testosterone therapy, after which it will recur for a second time; it will re-regress after adrenalectomy or hypophysectomy. Boyd[1] has remarked, "how can we draw a satisfying conclusion from such an array of confusing facts?"

TABLE 3 *(continued)*

Regression of liver metastases and primary after biopsy of liver	3 neuroblastomas
After partial excision of primary	4 neuroblastomas, 1 choriocarcinoma, 4 sarcomas
After attempt to excise primary	1 choriocarcinoma
After excision of large abdominal wall metastasis	1 melanoma
After celiotomy: gastroenterostomy	3 stomach
Irradiation	
To abdomen without benefit	1 neuroblastoma, 2 testicular, 1 ovarian
To mediastinal mass	1 neuroblastoma
To subcutaneous nodules without effect	2 neuroblastomas, 1 melanoma
Metastatic regression after irradiation to primary	3 choriocarcinomas, 1 sarcoma, 1 bone sarcoma
Metastatic regression after irradiation to another metastasis	1 melanoma, 2 choriocarcinomas
Regression of pulmonary metastasis after irradiation to pituitary gland	1 melanoma
Infection	
After varicella	1 neuroblastoma
After abscess near mass that regressed	1 melanoma, 2 colonic
After postoperative fever	3 sarcomas
After wound infection	1 sarcoma
Drugs	
After several courses of HN_2	1 neuroblastoma
After chlortetracycline	1 choriocarcinoma
After triethylenemelamine	1 neuroblastoma
Eliminate Carcinogens	
10 of 13 cases of bladder cancer after simultaneous transplantation of ureter, cystectomy in 9:	4 no microscopic evidence 5 microscopic evidence regression 4 months later
no cystectomy in 1:	
2 additional patients with staged transplantation of ureters exhibited regression: residual microscopic cancer	residual microscopic cancer in 1, none in the other

In several patients of our series, the existence of an hormonal factor appears to have been an important factor in the regression. For example, five ovarian adenocarcinomatous metastases regressed after excision of one or both ovaries. One breast cancer regressed after menopause, and one sarcoma regressed after a period of amenorrhea. Metastases from one sarcoma and three melanomas regressed after delivery of a child. Metastases from an adenocarcinoma of the kidney regressed after implantation of testosterone, and metastases from one choriocarcinoma regressed after 200 mg testosterone; after prednisone, metastases from one adenocarcinoma of the kidney and two neuroblastomas regressed. Metastases from three adenocarcinomas of the kidney regressed after synthetic progestational agents.

Chemotherapy

Although a cure from chemotherapeutic agents is not considered valid, this author will concede that the regression of the three patients after the three drugs mentioned may have truly been examples of unusually effective drug therapy.

Elimination of a Carcinogen

The importance of this factor as a causative agent in the development of spontaneous regression will be discussed later.

Miscellaneous Factors

In addition to the factors mentioned above, extreme *malnutrition* was present in three patients with cancer of the breast, three with cancer of the ovary, and two with cancer of the colon. It is doubtful that malnutrition could be primarily responsible for regression; however, because this was a factor in eight patients, these cases should be mentioned. *Interference* with the vascular supply, with consequent impairment of the nutrition of the tumor, has been listed as being a likely explanation for many cases of spontaneous regression. This would seem to be particularly possible when a tumor had been removed subtotally or when an attempt at removal was unsuccessful; many cases of spontaneous regression of neuroblastoma might be included in this category. I doubt, though, that this is the cause of the regression in many cases. *Unusual* sensitivity to usually inadequate therapy (especially chemotherapy) might be the explanation in a few cases. Also, one must always admit the possibility of *incorrect* histological diagnosis, even though two or three pathologists may have agreed to the diagnosis of malignancy.

Discussion

Factors That Affect the Growth and Spread of Cancer

In discussing spontaneous regression, it would appear appropriate to present some of the factors that affect the growth and spread of cancer, because these factors are obviously related to this phenomenon, although in an inverse manner. That is, regression occurs when the factors that cause the growth are no longer present. This might allow one to formulate some theories on the cause of spontaneous regression, even though one might have little or no evidence for the validation of these possible causes.

For decades, it has been known that growth and regression of a tumor were dependent upon virulence of the tumor and host resistance. As the study of tumor growth receives more attention, it becomes increasingly apparent to the author that the latter is far more important than virulence of the tumor. Host resistance is related to innumerable factors: antibody, hormonal cytotoxins not identified as antibody, certain blood cells (lymphocytes, histiocytes, immunoblasts, macrophages, and others) chemicals of the enhancing or inhibiting types, enzymes, "helper" or antagonistic viruses, physical agents, and so on.

Immunologic Factors

In my opinion, this group of factors is definitely the most important.

The Antigen-Antibody Complex. It has been only during the past 10 to 15 years that immunologists have conceded the presence of antigens in tumors. Because there is considerable difference between animals and human beings in this phase of resistance to tumors, they will be discussed separately.

In animals, as might be expected, the presence of antigens and antibody was developed earlier than in the human being. Gross,[13] in 1943, was probably the first to find the production of antibodies; he reported the regression of an intradermal sarcoma in mice by injection of diluted doses of a 20% suspension of sarcoma cells into the skin. Baldwin,[14] in 1955, reported the production of immunity to methylcholanthrene-induced tumors in rats after atrophy and regression of implanted tumors. Prehn and Main,[15] in 1957, described the discovery of tumor-specific antigens in carcinogen (methylcholanthrene)-induced neoplasms of inbred mice. Later, they indicated that specific antigens were found in almost every animal neoplasm, including those induced by viruses, chemical carcinogens, and certain spontaneous animal tumors. In 1961, Old and associates[16] found nonspecific stimulation of the immune system of mice by inoculation with Bacillus Calmette-Guérin (BCG). Haddow and Alexander[17] discussed how partial removal of tumors induced by benzpyrene, irradiation of them, and frequent subcutaneous inoculation retarded the growth of the remaining tumor, in contrast to the controls.

Hellström and Hellström[18] have conducted extensive experiments in tumor-specific transplantation antigens (TSTA) and have noted that almost all animal neoplasms studied contained them. Alexander and Hall[19] have indicated that rats with primary fibrosarcoma that was induced chemically did not develop blood-borne metastases until the antibody was absent. Klein and Oettgen[20] found increasing evidence that primary tumors evoke both antibody-mediated and cell-mediated immune reactions in their own hosts.

In the human, Graham and Graham[21] were among the first to offer laboratory evidence of antigenicity. They reported that 12 of 48 patients with cancer of various types had circulating antibody to their own tumor. Furthermore, most of the patients who did not possess the antibody had advanced cancer. Klein[22] emphasized that immune responses by the host against tumor-associated antigens have been demonstrated in nasopharyngeal cancer, Burkitt's lymphoma, malignant melanoma, neuroblastoma, osteogenic sarcoma, and cancer of the colon and bladder. Of great interest are the studies of Morton and associates,[23] which showed that a rise in antibody titer occurs after surgical removal of the tumor mass in skeletal and soft tissue sarcoma. Furthermore, all patients with recurrent disease had a progressive decline in their titer with advancing disease. Woodruff[24] has suggested that perhaps all malignant tumors possess specific antigens in the early stage of the disease, but with passage of time these antigens are somehow deleted or diminished in amount. This would help to explain why most tumors grow slowly at first but later metastasize and grow rapidly.

During the past few years, several clinical groups have initiated immunologic therapy of various types. Krementz and colleagues[25] irradiated 30–160 $\times$ 10^6 cancer cells with 10^4 to 5 $\times$ 10^4 r and injected them intradermally into numerous areas of the body. Only the first of 19 patients so treated displayed a total disappearance of the melanoma tumor up until the time of his death 4 years later. They reported that five of 58 patients treated by four methods of immunotherapy had complete remission for 3 months to 3.5 years. Morton and Eilber[26] injected BCG vaccine into eight patients with malignant melanoma, with consequent regression or disappearance of the skin tumors in five of the eight. Humphrey and associates[27] prepared and administered a vaccine by alternately freezing and thawing a homogenate of tumor tissue. A few patients were given this vaccine subcutaneously and intradermally, which was made from a tumor other than their own. In a few patients, they exchanged plasma and leukocytes. Of 54

patients available for analysis, 13 demonstrated a decrease in size of their metastases. The sera of 50 patients were tested against tumor cells; activity against tumor cells was noted in 24 of the 50.

Because the immunologic effects of antibody and cellular elements are limited (cell-to-cell basis for the latter?), Woodruff[24] has recognized the limitations of immunology and has suggested that the most practical use of this therapy would be on patients *after* surgical excision of the primary lesion, which hopefully would destroy microscopic cells that remained. Numerous immunologists have made a similar suggestion.

Cellular Elements Involved in the Immune Process. Of all the cellular elements that reveal immune activity, the lymphocyte is apparently the most important. Hellström and coworkers[28] examined peripheral blood lymphocytes in 373 patients with a malignant tumor. The patients were tested either for colony inhibition or cytotoxicity for cell-mediated immunity against various types of human tumors. Lymphocytes from 51 to 59 patients either reduced colony numbers formed by autochthonous tumor cells or were cytotoxic to them. It was also noted that lymphocytes from 78 to 87 patients displayed a similar effect on allogenic tumor cells of the same histological type as those of the lymphocyte donor. "Evidence indicating antigenic cross-reactivity between tumors of the same histological types were obtained for the following seven groups of neoplasms; malignant melanomas, cancer of the colon, breast, testis, endometriun, ovary and various sarcomas." Also, 11 of 12 patients tested after a symptom-free existence for more than 2 years still exhibited lymphocyte-mediated antitumor immunity.

Hellström and Hellström[29] have found that lymphocytes from patients with neuroblastoma were inhibitory to the growth of neuroblastoma cells. They also noted that "lymphocytes from patients with progressively growing tumors were capable of destroying cultured tumor all to approximately the same degree as lymphocytes from clinically symptom free patients." Alexander[30] stated that "cytotoxic immune lymphoid cells have the capacity for traversing capillary beds, and they can thus bring immune reactions to extravascular spaces."

Moore and Gerner[31] described infusing large quantities of either autochthonous or allogenic lymphocytes into 31 patients with advanced cancer, 10 of whom had significant remissions.

Alexander and Hall[19] indicated that "non specific stimulation by B.C.G. may increase the number of macrophages" and that inflammation induced in the vicinity of the tumor may aid in the disappearance of the tumor. They quote Gorer[32] as being the first to observe that "all such procedures bring macrophages into the vicinity of the tumor."

During the past few years, the number of immunoblasts in the thoracic duct lymph under various circumstances has been studied by numerous investigators; several workers have discovered that when a syngenic tumor is implanted into a rat the number of immunoblasts increases, although this may not persist. Alexander and Hall[19] noted that in rats with primary or established syngenic grafted tumors that were growing below the level of the diaphragm, the number of immunoblasts in the thoracic duct lymph was practically normal. Within 24 hr of the excision of the tumor, however, there was a sudden increase in the number of immunoblasts in the thoracic duct lymph. They concluded this was a specific response, because it was not seen after a sham operation or removal of half of the tumor. In their opinion "the immunoblasts must have been present in the lymph nodes all the time, but the presence of a large tumor mass was exerting some influence that prevented their release into the lymph." Does this observation

denote that the presence of large masses of tumor (primary or otherwise) interfere with the immobilization of immunoblasts?

Draz and colleagues[33] have found that histiocytes from isolated guinea pig liver and spleen are capable of removing tumor cells from perfusate that contains tumor cells. In addition, histiocytes from tumor-immunized guinea pigs exhibited an increase in histiocyte tumor phagocytosis in both organs, compared to non-immunized animals.

The Role of Immunoglobulins. Witz[34] has analyzed the tissue of primary benzo [*a*]pyrene-induced sarcoma and has found that it contained at least 10 times more immunoglobulin than normal tissue. He noted that higher immunoglobulin IgG_2 fractions were eluted from fast-growing tumors and from primary rather than secondary tumors. He suggested that tumor-associated immunoglobulin IgG_2 may represent specific antibody directed against determinants of tumor cells. Takasugi and Hildeman[35] have found that hyperimmune serum produced in host mice against allogenic tumor antigens inhibited and enhanced tumor growth. They stated further that "Fractionation of the antiserum of column chromatography established that immunoglobulin M was primarily responsible for inhibition, and immunoglobulin G2 for enhancement." Stuart[36] described an irregular but definite rise in immunoglobulin levels in reticulum cell sarcoma; all the immunoglobulins were affected.

Blocking and Unblocking Agents. Hellström, Sjögren, Warner, and Hellstrom[37] found that sera from tumor patients would block the cytotoxic effects of lymphocytes immune to the specific antigen of the respective neoplasms. The "sera from 67 of 81 patients with growing neoplasms were found to block the cytotoxic effects of specifically immune lymphocytes. A blocking effect was seen, both when the tumor cells, lymphocytes and sera were taken from different donors who had the same types of tumor as target cells." No blocking was seen when the same sera were tested on tumors of histologic types other than those of the respective serum donors. Blocking serum activity was found in only three of 19 patients who were symptom free after tumor therapy. These data suggest that there is a correlation between tumor growth *in vivo* and the presence of a blocking serum activity *in vitro*. These workers indicated that "blocking factors can be eluted from human tumors removed at surgery;" from animal experiments, they believe that the blocking factor "may be antigen-antibody complexes." In one of their patients with metastasizing melanoma, the serum was blocking when first tested, but afterward the blocking activity disappeared, at which time a remission of the melanoma occurred. Serum obtained after the remission had an unblocking activity "similar to that seen with certain animal immune sera in that it could abrogate the blocking effect of serum from other melanoma patients." Sjögren and Bansal[38] believe that the unblocking factors found in the rat polyoma system are immunoglobulins. Sinkivics and associates[39] reported that three of their patients with disseminated sarcoma "circulated serum factors that specifically antagonized the cytotoxic effects of lymphocytes on sercoma cells," but "after chemotherapy (the main agent was cytosine arabinoside) the blocking factors became undetectable."

The Significance of Immunosuppression. For several years, evidence has gradually accumulated that suppression of immunologic activities in the human by immunosuppressive drugs after kidney transplantation lowers the resistance of the recipient to cancer. For years it has been known that newborn mice are extremely susceptible to the development of malignant tumors after the injection of causative agents such as carcinogens and viruses, but they often are completely

resistant when injected as adults, thus demonstrating that mice develop an increased resistance to tumors as they mature. For example, Allison[40] has shown that the incidence of tumors after injection of polyoma virus to newborn mice is high, but that it is low if the inoculation is made in adult mice. When he produced immunosuppression by thymectomy at 6 weeks of age, inoculated the mice with polyoma virus, and then gave weekly injections of A.L.S., all the mice developed polyoma tumors.

Starzl and associates[41] found that in 189 of their patients under immunosuppressive therapy for preservation of the transplanted homologous kidney, 10 (5.3%) developed malignancy (seven cancers and three mesenchymal malignant tumors). Doll and Kinlen[42] indicated that of over 4000 kidney transplanted up to 1970 (Penn), at least 40 primary malignant neoplasms have been reported. They estimated that the increase in mesencymal malignant tumors (sarcomas) in themselves had increased in the recipients by 50-fold. In addition, these workers reported that seven of the examples of malignancy occurred in recipients of kidneys from patients who were dying from malignant disease. In some of these cases, cessation of the suppression was succeeded by disappearance of the metastases.

This marked increase in the incidence of malignancy in the recipients of transplanted kidneys under immunosuppression indicates clearly that some humans lose enough of their normal protective mechanisms while under this immunosuppression that malignancy develops spontaneously. This suggests that cancers may be frequently produced in our bodies from time to time but that our defense mechanisms destroy the malignant cells.

Hormones

The hormone dependency of numerous tumors has been recognized for decades. For example, 25–30% of women with cancer of the breast will sustain an appreciable regression after male hormone therapy; this remission may last for 3 months to 2 years. Similarly, if adrenalectomy or excision of the pituitary gland is performed on similar patients, a regression is also sustained. In addition, 25–30% of patients with carcinoma of the prostate will incur regression after orchiectomy and administration of female hormone therapy. Unfortunately, none of these regressions are permanent.

Enzymes

Few scientists have suggested that enzymes exert a significant role in the growth of cancer, but recently some enzymes have been described as possessing the potential to interfere with cancer growth. For example, Currie and Bagshawe[43] noted that when viable tumor cells (methylcholanthrene-induced sarcoma) are incubated with neuraminidase, the incidence of successful transplantation into syngenic animals is reduced. Simmons and associates[44] described how neuraminidase enhances the immune response in mice to sarcoma and spontaneous mammary carcinoma, and causes regression of established animal neoplasms by active immuno therapy. L-Asparaginase is also a tumor-inhibiting enzyme. Several RNA tumor viruses contain polymerase enzyme, which can reverse the normal direction of cell life.

Elimination of Carcinogen

Although few examples (except the regression of cancer of the bladder by elimination of carcinogen as herein described) have been reported, this possibility appears worthy of consideration as discussed later.

The Possible Role of Interferons

Wagner[45] has defined interferons as a "chemically heterogenous class of proteins" that have a "capacity to inhibit viral multiplication." This action would presumably limit its use for treatment of cancer to those tumors caused by viruses. Even then, its action might not be effective in treatment because interferon has no significant cell toxicity, even though its site of action is intracellular, not extracellular. It is apparently not present (in detectable amounts) in normal cells; "its production is induced by viral infection or by exposure to a variety of non viral substances, including nucleic acids and bacterial endotoxins."[45] To exert a significant role in the destruction of cancer, the tumor would have to be of viral origin, and the life and growth of the tumor would have to be dependent upon the continuing growth of the virus. With the present knowledge of cancer growth, it would not appear probable that one could destroy cancer with interferons, without destroying any normal tissue. Yet, there is no concrete evidence that can eliminate the possibility of usefulness.

Theoretical Factors Possibly Responsible for Spontaneous Regression

As far as this author is aware, there is not a single valid explanation for spontaneous regression of cancer. After surveying the data in our monograph,[5] about the only information that appeared reasonably valid was the assumption that there are numerous causes of spontaneous regression, as has been emphasized by Boyd[1] and others. Because factual data is rarely accumulated without the development of theories, it would appear appropriate or mandatory that theories be devised and explored in a subject that has had little or no explanatory contribution since it was recognized many years ago. Similarly, it is quite possible that unorthodox ideas might be the most productive.

There can be no doubt that most human beings have a certain amount of resistance to their cancer. In only a few patients does the tumor grow so rapidly that there appears to be no resistance. In general, one assumes that if a patient fails to show gross metastases within 3 years after removal of the primary lesion, the patient's resistance has held the tumor in check. Because many patients (more than half) survive more than 2 years without evidence of metastases, a certain amount of resistance in the human must be the rule *not* the exception. This statement is made with the realization that nearly all patients in the 5- and 10-year class of survival have had cancer cells escape from the primary lesion before the definitive therapy had been performed. In the so-called "cured" patient, the patient's resistance either destroyed the cells that escaped from the primary tumor or maintained them in a noninvasive state. Some shrewd clinicians[46,47] have reported patients of this type who had been free of metastases for 15–20 years, only to develop rapidly fatal metastases after some type of stress or shock that apparently reduced the resistance sharply.

Alteration of the Tumor-Host Relationship

Is it possible that when spontaneous regression occurs, the host resistance has been heightened by a tumor antigen that has undergone alteration or modulation, with a resultant increase in the immune response to the tumor antigen? This appears to be one of the most significant possibilities. There are many ways of effecting this to a slight extent in animals, for example, with iodoacetate and other reagents,[48] to increase the antigenicity of animal tumors, but no real efficient mechanism has been reported.

A second possibility might be the mechanism of nonspecific stimulation of a flagging tumor-specific immunity. If one believes that the cancer patient has some resistance, but the patient with increasing tumor growth has inadequate resistance, any stimulant that speeds up the immunologic motor may also speed up the specific tumor immunity. Examples of such immunologic adjuvants are BCG vaccine, Freund's adjuvant, and the methanol-extractable residue of tubercle bacillus. Could the patient encounter chemicals in everyday life that act as BCG or Freud's adjuvant? Because these substances are simple ones that contain bacterial elements, it does not appear impossible that the patient may ingest something similar, something far more potent than the tubercle bacillus. This possibility cannot be ignored as a cause of spontaneous regression.

The unblocking activity as outlined by the Hellström group could easily exert a role in spontaneous regression, especially because it may be due to immunoglobulins (Sjögren and Bansal[38]). True, this unblocking activity may be no more than antibody excess. Nevertheless, one would presume that the antibody stimulated to excess must be cancer specific to exert its effect.

In a few of our patients, the regression was preceded by (or associated with) fever or an abscess, particularly in cancer of the colon and sarcoma. This happened often enough to make me think that there was a relationship to the regression. The infection may exert this effectiveness by either altering the cancer antigen or by nonspecifically enhancing a specific tumor immune response, and this could thus logically occur as described above.

The many patients in our series who displayed regression of metastases after irradiation of a distant metastasis or exhibited regression of a mass after irradiation with no more than a few hundred roentgens, leads me to conclude that at one stage of its growth the tumor was unusually sensitive to the irradiation. This end result may have occurred because the radiation increased the antigenicity of the tumor and thus stimulated a heightened immune response. Conversely, maybe in a very sensitive tumor irradiation decreased the mass of the tumor and lowered the number of tumor cells below the critical level, so that the present, but weak, immune response could destroy the rest.

Ten of our patients underwent an unsuccessful attempt by a surgeon to remove the tumor. All surgeons know that this procedure is usually followed by an increased growth of the tumor. Yet, under these circumstances, the reverse happened. Let me paraphrase Boyd: "How can we make sense out of so many confusing facts?" Could it be because the antigen was changed by exposure of raw tissue to the active tumor tissue in such a way that enhancement of the immune response resulted? This is a plausible explanation, but one could also evoke others, for example, the increased vascularity stimulated by dissection around the tumor invoked a greater quantity of immune factors, or a rebound of immunity after the suppression of host resistance which might be produced by anesthesia and surgery.

Elimination of the Carcinogen

As stated previously, about the only real clue of an explanation for spontaneous regression occurred in our group of bladder cancers. Because 10 of 13 cases regressed after bilateral transplantation of the ureters, there appears to have been something in the urine either responsible for the development of, or the continuing growth of, the bladder cancer. Also, because in an additional two cases the tumor regressed after transplantation of one ureter, the human body must have a certain amount of resistance to cancer—enough to cause regression if only a part of the

causative agent was removed from contact with the tumor site. In these 12 patients, I have assumed that the causative agent was a carcinogen; this is purely an assumption, however, because the agent might have been a virus. In either case, it is inconsistent to have the tumor disappear in a few weeks or months when in the usual example of tumor caused by a carcinogen many years are required for appearance of the tumor. Perhaps the immune response was so intense in these 12 patients that the tumor was destroyed once the causative agent (carcinogen?) was eliminated from the tissue that was prone to develop cancer (the bladder mucosa). In our series, I was unable to find a possible source of carcinogen in a single case. This may not indicate much significance as one is aware of the formation of intrinsic carcinogens (no doubt many more unknown) that would not allow detection by methods now available. Another feature that is difficult to understand is that cessation of cigarette smoking does not allow lung cancer to regress, even though we are relatively positive about the etiologic significance of the cigarette. It appears logical to this author that by a change in habits the patient might avoid a carcinogen (unknown to us) with a resultant regression.

This information alone, meager as it is, indicates that in the treatment of cancer, even in an individual case, the investigator should devote more attention to finding a causative agent such as a carcinogen or virus.

Effect of Excision of Primary Tumor on Metastases

Although the most common factor related to spontaneous regression in our monograph was excision of the primary (41 cases), I cannot attach much importance to it because metastases develop so commonly after excision of the primary. This relationship, however, occurs too often in our 176 cases to ignore it; if it is related to regression, it would appear that the most probable cause would be a specific action on the antigen or enhancement of the immune response to the tumor antigen.

Viral Interference or Viral Antagonism

For this phenomenon to be related to regression of tumors, a virus would have to be involved in the etiology. We have modest evidence that viruses exert a role in the etiology of the leukemias but little evidence in solid tumors. I believe that they are of etiologic importance in solid tumors, however, even though they may be synergistic to carcinogens.

During the past 20 to 25 years, so many viruses with so many different actions have been discovered that antagonistic viruses would be expected. Such antagonism is well known in the bacterial world (giving rise to antibiotics). Why not in the viral world of tumors? In fact, this antagonism has been reported. In 1937, Levaditi and Haber[49] noted that a mouse virulent fowl plague virus had a necrotizing effect on a transplantable mouse tumor. This tumor destruction was noted histologically and by the failure of infected transplants to grow. However, the mice so inoculated invariably died of the viral infection. These investigators apparently thought that some sort of contributory aid was furnished by the host.

Sharpless and associates[50] tested several viruses against a transplantable lymphoid chicken tumor. Some of the animals survived the viral treatment of their tumor, and later it was shown that they were refractory to reimplantation with the same tumor. The production of immunity by their viral treatment is somewhat clouded, because older animals often rejected the tumor spontaneously and were thereafter immune to reimplantation of the tumor. This experiment, how-

ever, demonstrated the ability to treat a tumor successfully with a virus, without a lethal outcome.

Of equal importance are the experiments of Ginder and Friedewald,[51] who found that rabbit fibromas induced by the intracutaneous injections of Shope fibroma virus could be destroyed by the Semliki forest virus during the first 48 hr of tumor induction. It appears that the tumor cell loss was produced by destruction or necrosis caused by the superinfecting virus. Again, this is a tumor against which the host displays defense strong enough to cause regression.

More recently (1965) Molomut and Padnos[52] described the discovery of a new virus (designated as the M-P virus) in mice that does not induce any cytopathic changes in normal mouse cell cultures, and when injected into susceptible mice this virus induces a viremia that suppresses transplanted and spontaneous tumors. In fact, the suppression of spontaneous leukemia in AKR mice was almost complete (46 of 47 mice). This virus in infective for rats, young cats, and dogs; it produces symptoms similar to those found in mice during the acute viremia, with no evidence of disease.

Taylor and coworkers[53] demonstrated that treatment of mice that possess sarcoma-1 and Ehrlich ascites carcinoma with bovine enterovirus-1 resulted in regression of the tumors, without any damaging effect on the animals. In addition, death of mice with lymphatic leukemia L4946 was delayed by this treatment. These workers do not believe that the oncolytic activity is related to the production of interferon but instead that it requires specific absorption of virus to the tumor cells. The oncolytic action extends to cells in culture. A virus of this type appears to offer promise in human disease and could easily explain some cases of spontaneous regression of either the temporary or permanent type.

Wheelock and Dingle[54] determined that the administration of numerous viruses to a patient with myelogenous leukemia provided a benefit after each inoculation. The viruses used were Sendai virus, Newcastle disease virus, influenza A and B viruses, Semliki forest virus, and Sindbis virus. They concluded that because remissional benefit occurred after the inoculation of each virus, this was statistically significant. This is a different reaction than described in the above reports. The authors believed that the viruses stimulated some type of protective mechanism. Did the viruses result in the restoration of a protective function destroyed or damaged by the leukemic disease? The patient was described as moribund when the inoculations were started.

The examples of viral interference or antagonism mentioned above are only a few of those available in the medical literature. In fact, there are so many such reports that a certain amount of validity must exist. This phase of viral activity must be investigated further.

Hormones

Theoretically, hormones should be the most important group of substances likely to produce spontaneous regression, because organ ablation (ovary, adrenal, and pituitary gland) and the male and female hormones are used extensively and with a fairly high percentage of short regression (20–30%). However, this author does not believe that they are often responsible for spontaneous regression, particularly because the tumors most commonly considered to be hormone dependent are not those that were most frequently encountered in our series of 176 cases. Moreover, only two or three patients revealed their spontaneous regression during or shortly after menopause.

Miscellaneous Factors

The rapid accumulation of data during the past 10 years including the immunologic effect of cellular elements, such as immune lymphocytes, macrophages, immunoblasts, and others, makes it essential that they be considered as likely causes of spontaneous regression. If they were a common cause of regression, though, one would expect that these cells must be present in countless numbers (based on the cell-to-cell concept of destruction)—so many that at least a few of the authors who reported these cases should have observed them.

Drugs or chemical compounds of countless types must be considered as a possible cause, perhaps on the basis of stimulation of the immune response to the tumor antigen. I may have only slight justification for consideration of drugs, as our laboratory, and many others, have reported that certain types of stress[12] (celiotomy, chemical damage of the liver and spleen, and so on) will reduce the resistance of animals to cancer cells. Buinauskas and colleagues[55] examined the effect of innumerable compounds on the resistance-decreasing phenomenon. Of all the compounds used, reserpine (serotonin antagonist) was the only drug that prevented the decrease in resistance to cancer cells that develops after the stress of celiotomy. With this action in mind, it is not impossible to postulate that certain chemicals may alter the cancer antigen or stimulate the immune response to the tumor antigen.

The recent reports that a *combination* of modalities, such as surgery, irradiation, and chemotherapeutic drugs (or simply a combination of drugs), will improve the 5-year survival results justifies the thought that a combination of unknown or undiscovered factors may be able to produce a regression. Duran-Reynals[56] has reported that chemical carcinogens and viruses may act synergistically.

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