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## Significance of spontaneous regression of malignant disease

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**THE SIGNIFICANCE OF SPONTANEOUS  
REGRESSION OF MALIGNANT DISEASE**

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## CONTENTS

Introduction. . . . .	1
Case Reports. . . . .	4
Discussion. . . . .	.10
Conclusion. . . . .	.14
Summary . . . . .	.15
Bibliography	

## INTRODUCTION

It has been estimated that, in 1962, approximately 520,000 people will discover that they have cancer; the number of deaths due to cancer in this year may be close to 300,000. Cancer is not only a leading cause of death, but also a dreaded disease. The psychological impact on both the afflicted and his family, the suffering of pain, and the ever-present doom make it a much feared disease...wide publicity, for purposes of educating the public in order to encourage early diagnosis, has possibly contributed to this fear.

Great therapeutic strides have been made, and in recent years the prognosis in many cases is improved. However, the cause of cancer and its cure based on cause is still unknown. It is for this reason that the spontaneous regression of a malignant growth, is such an intriguing and challenging phenomenon; it gives us hope for more effective means of treatment than our present tools--surgery and radiotherapy.

The incidence of spontaneous regression has not been well established, and those making an estimate are a brave minority. Bashford<sup>1</sup> estimates 1/100,000, and Boyers<sup>2</sup> estimates 1/80,000. Some authors deny that such regression exists<sup>3</sup>. The problem is made difficult because the growth rate of the different types of cancer

varies greatly as do the growth rates of specific types of cancer. Criteria and definitions are therefore, important.

Spontaneous regression (S. R.) is usually defined as the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant effect of regression or destruction on neoplastic disease<sup>4</sup>. This definition does not imply that S. R. is synonymous with cure; in some cases quoted, tumor which regressed in one area, grew unchecked in other areas.

Definite criteria are also important in evaluating this concept. Adequate histo-logic examination of the primary and of metastatic lesions is practically mandatory and certainly best. Pathologic slides should be saved and put on record and made available to common scrutiny. In some cases, only clinical evidence of S. R. can be given; therefore the following categories of S. R. are usually offered:

- (1) Regression of primary tumor.
- (2) Regression of metastatic tumor (histologic confirmation of metastasis)
- (3) Regression of metastatic tumor (no histologic confirmation)...here the S. R. of lesions may be questionable because the malignant nature of the metastases is observed by gross appearance only; although it is presumed primary, it is proven malignant histologically.
- (4) Regression of presumptive metastases as diagnosed by roentgenograms. (Again questionable and without histologic proof of malignancy.)

- (5) Prolonged arrest of growth of cancer.
- (6) Prolonged latent period between development of primary tumor and evidence of recurrent or metastatic cancer.

These last two categories only offer support to the thesis of possible biologic control of cancer. They do not present evidence of S. R.<sup>6-7-8</sup>, and warning is made that such reported cases may fall into the unpredictable nature of the natural course of any individual case of cancer.

There are other reasons to exclude cases from such a series. Controversial histologic diagnoses of malignancy are eliminated. Publications prior to 1900 are usually not acceptable because of the much greater possibility of inaccurate histologic diagnosis. Epitheliomas of the skin are eliminated<sup>9</sup>. Tumors that could have not been clearly illucidated, and which later may reveal added cases, are not included. Finally, many cases, in regard to lymphomas have not been thoroughly surveyed and reviewed. More and more cases are being uncovered ~~that~~ fall under the class of spontaneous regressions. In 1956, in a preliminary report, Everson and Cole<sup>10</sup> had investigated 600 cases, 47 of which complied with the above criteria. Later, in 1959, they<sup>11</sup> had reviewed over 1,000 cases and had increased their series to 112. Interest is quickening in spontaneous regressions.

## CASE REPORTS

The following case histories are cited in hopes of illustrating what is meant by spontaneous regression. This list is by no means complete and is not intended for such a purpose.

Case No. 1: The patient is a 56-year-old male who underwent urological examination, including bladder mucosa biopsy in 1948. The histologic diagnosis was adenocarcinoma of the bladder. Ureterosigmoidostomy was performed as the extension of growth made resection of the tumor inoperable. Cystoscopic examination 50 days post-op demonstrated normal bladder mucosa. Cystectomy was then performed, and no gross evidence of tumor was found. However, cancer cells were present in tissues underlying the mucosa.<sup>12</sup>

Case No. 2: Histologic diagnosis of biopsy tissue was papillary carcinoma in a 60-year-old white male. Treatment given was ureterosigmoidostomy only. At cystoscopic examination 71 days post-op, only normal bladder mucosa was demonstrated. Cystectomy was then performed, and no gross evidence of tumor was found; however, cancer cells were present in the tissues underlying the bladder mucosa.<sup>12</sup>

Case No. 3: This is a case of papillary carcinoma occurring in the bladder of a 66-year-old man. Diagnosis was made by biopsy

in 1948, and was followed by ureterosigmoidostomy. Cystectomy done two months after this operation revealed only normal appearing mucosa by gross examination. The growth biopsied was 3-cm. in diameter before transplant of ureters. Histologic examination of removed bladder revealed carcinoma cells in the muscle layer.<sup>13</sup>

Case No. 4: Papillary carcinoma of the bladder was diagnosed in 1948 by biopsy and histologic examination. Cystectomy performed six months later failed to reveal any presence of tumor.<sup>13</sup>

Case No. 5 Transitional cell carcinoma of the bladder was discovered in a 55-year-old male. Diagnosis was made in 1950 by biopsy and was followed by ureterosigmoidostomy. Three weeks later, after cystectomy, histologic examination failed to reveal any malignant growth present in the bladder.<sup>14</sup>

Case No. 6: Squamous cell carcinoma of the bladder was diagnosed in a 34-year-old male in 1953. Biopsy and ureterosigmoidostomy were followed by cystectomy four months later. There was no histologic evidence of tumor at that time.<sup>10</sup>

Case No. 7: Transitional cell carcinoma of the bladder was biopsied from a 62-year-old male in 1953. Ureterosigmoidostomy was performed. At autopsy, 17 days after ureterosigmoidostomy, histologic examination of the bladder failed to demon-



strate a tumor.<sup>10</sup>

Case No. 8: Papillary carcinoma of the bladder, biopsied in 1951 from a 55-year-old male, was followed by uretero-sigmoidostomy. At autopsy, 39 days later, histologic examination failed to demonstrate any malignant tumor of the bladder.<sup>15</sup>

Case No. 9: Scirrhous cancer of the breast in a 37-year-old female was treated by mastectomy in 1904. Diagnosis was confirmed by histologic examination of the tissues removed. By 1907, large axillary and local masses not removed at the time of surgery had disappeared.<sup>16</sup>

Case No. 10: A carcinoma of the breast in a 37-year-old female was treated by radical mastectomy. Five years later, secondary growths in the neck, scar, and liver had disappeared or decreased.<sup>17</sup>

Case No. 11: A scirrhous cancer of the breast was treated by radical mastectomy in 1907. Local recurrences were incompletely removed shortly thereafter. The local recurrence residual disappeared without further treatment, until 1913.<sup>18</sup>

Case No. 12: Carcinoma of the breast was treated by radical mastectomy. Nodules noticed in the healing scar and the development of a stony, hard hepatic enlargement were not treated. Soon after, these findings disappeared without further evidence of recurrence.<sup>19</sup>

Case No. 13: Adenocarcinoma of the descending colon was discovered in a 45-year-old man. Curettage of two abdominal sinuses and a right transverse colostomy was performed. Material removed from the sinuses revealed adenocarcinoma, probably of intestinal origin. Fever was present. Three-hundred roentgens of x-ray was administered to the sinus areas. Two years later the mass had disappeared and at celiotomy, no evidence of previous lesions were found. Six cm. of descending colon was absent. No tumor tissue was found on microscopic examination of the two blind ends of the descending colon.<sup>20</sup>

Case No. 14: Adenocarcinoma of the rectum with recurrence at the site of the colostomy. At the time of removal of the recurrence, there were nodules along the pelvic brim and large nodes present in the mesentery. Twenty-seven months later, and 20 months after a febrile episode, abdominal exploration revealed no evidence of tumor. Numerous biopsies were histologically negative.<sup>10</sup>

Case No. 15: Hypernephroma of the left kidney was treated by surgical removal of the tumor. Inspection of the specimen revealed entire tumor mass calcified except for one small piece of tissue the size of a marble which was histologically diagnosed as hypernephroma.<sup>2</sup>

Case No. 16: Hypernephroma of the left kidney was removed sur-

gically from a 45-year-old female. The tumor was completely separated from kidney substance and lying free in the cavity in the upper pole of the kidney. No vascular connection was seen with the kidney. Microscopic picture was typical for hypernephroma although the nuclei of the cells took the stain poorly.<sup>21</sup>

Case No. 17: Neuroblastoma was diagnosed in a month old infant. Treatment consisted of biopsy of subcutaneous nodules and small amounts of nitrogen mustard, with no immediate effect. Six weeks later the abdominal mass began to shrink, and cutaneous lesions began to disappear. Seven months after biopsy only two cutaneous nodules were present out of many previously. Also, the abdominal mass was much smaller.<sup>4</sup>

Case No. 18: Neuroblastoma was diagnosed by biopsy of a lesion in the femur at infancy. X-ray to the femur was the only treatment as the site of the primary was unknown. At age 14 years, no evidence of metastatic of primary tumor had occurred.<sup>4</sup>

Case No. 19: Neuroblastoma was diagnosed by biopsy of one of many subcutaneous nodules. Radium plaques were applied to one or two nodules. Also, a small amount of Coley's toxin was used. Examination five years later revealed no evidence of nodules or tumor.<sup>4</sup>

Case No. 20: Papillary adenocarcinoma of the ovary was diagnosed in a 58-year-old female, and treatment consisted of excision of the left ovarion tumor mass and the right normal ovary. At the time of operation three firm, raised nodules of one to one and one-half inches in diameter were present on the surface of the liver. Two and one-half years later, at a subsequent operation, the liver was smoothe and the only sign of three previous nodules was a puckered scar.<sup>22</sup>

Case No. 21: A myosarcoma of the uterus was biopsied and then treated with radium. No regression was noted with the radium treatments. The patient developed high fever and an allergic response. The tumor then completely disappeared. The patient is well, ten years later.<sup>4</sup>

## DISCUSSION

In considering the possible reasons for spontaneous regression, it appears thus far that no one factor seems to be the over-all determinant. First consideration is given to mistaken diagnosis, but recently great efforts to exclude this possibility have been made, and successfully so. All cases before 1900 have been excluded. Unless complete and adequate histologic interpretation is made, the case is not included.

Removal of a carcinogenic agent may be a possible reason. Case reports (one through eight) illustrate this point. Regression may occur after divergence of the carcinogenic agent, presumed to be in the urine. However, should not the supposed carcinogenic agent then stimulate malignancy in the bowel, to where it is diverted?

Interference of the nutrition to the tumor is postulated. During incomplete removal of a malignancy, compression or constriction of nutrient vessels could occur. It may also be possible that surrounding tissue and vessels through altered metabolism undergo hyaline degeneration with resultant calcification and encapsulation of the tumor.

What may be deemed as incomplete removal may actually be complete with the surrounding tissue being only inflammatory reaction. This argument appears particularly defective since it would appear

that this possibility could easily be determined simply by taking a sample of such tissue.

Some of the tumors, treated with an amount of radiation considered inadequate, regressed remarkably. This response could be due to unusual sensitivity to x-ray. This increased sensitivity also holds for radiation-like drugs. Case reports by Stewart, utilizing small doses of nitrogen mustard or minimal doses of x-ray, illustrate this possibility. One attempt made to increase the sensitivity is to perfuse the tumor site with hydrogen peroxide, while radiation therapy is being performed.

Allergic or immune reaction<sup>23</sup> with destruction of the malignant cells might be a factor in spontaneous regression. Stewart's case of myosarcoma of the uterus is an example. The immunity to cancer cell proteins is being increasingly investigated.

Endocrine influences are sometimes suggested as a possibility. Palliative effects of oophorectomy, adrenalectomy, and hypophysectomy on certain cancers are well known. It is postulated that when the metastases destroy hormonal influences, it destroys itself. However this theory does not explain regressions in tumors which are not thought to be hormone-dependent. Also, could it be possible that all tumors create a hormone of their own type? In certain cases some of the unexplained symptoms and signs such as hypoglycemia,

hypercalcemia, arthritis, and skin effects may be the direct result of some "hormone-like" product of the cancer cell.

Fever and/or acute infection are factors which are frequently implicated in cases of spontaneous regression. Furgeson and Black's case of inoperable cancer of the colon is used as an illustration. They believe that the areas of tumor became infected, and infarction with resorption followed.

Whichever factor is the correct one remains to be seen. Nevertheless, the existence of spontaneous regression in at least some cases, though it be few, supports the argument that biologic control of cancer can be obtained. It reinforces the hope that a more satisfactory method of treating cancer than surgery and/or radiation may be found in the future. The evidence, not presented here, that spontaneous regression occurs in the animal experimental laboratories, also lends encouragement to the possibility of experimentation in this field. It would be tedious work if the ratio of one case per 100,000 holds true. However, should't this ratio be the number of cases of spontaneous regression over the total number of cases not treated? Is not it possible that through our various methods of treatment, we are deterring the force or forces which tend to consume the malignancy which is consuming the person? To include all cases of cancer, treated and untreated, in the denominator seems unfair, particularly when cases deemed adequately treated are excluded

from the numerator.

At the same time that spontaneous regression springs hope, it serves as a precaution to claims of "cure". Great caution in the assessment of chemotherapeutic and unorthodox measures is mandatory. It is also worthy of remention that spontaneous regression is not synonymous with "cure".

Finally, spontaneous regression also has significance when talking to a patient with "hopeless cancer" about his prognosis. It is usually quite helpful to a patient and his loved ones when they are given the bright side of an already dismal picture. When current methods of therapy fail, one should not turn his back on the cancer patient. It is at this period when he needs support, "bedside manner", and "caritas medici" the most. A little bit of hope is invaluable therapy. When the disease progresses to painful suffering, the question often arises whether to "let the patient die". Beside the reason that death should not be utilized as an alternative for pain, it is not in the realm of knowledge of a practicing physician just when a spontaneous regression might occur.



## CONCLUSION

If it were known how to study these cases carefully and what studies to do, it would be possible to find out why spontaneous regression occurs; then we would have the answers to many questions concerning malignant disease. Experimentation of S. R. in the animal laboratory has already been alluded to. Great help could be obtained if complete cancer registries, such as in Connecticut, were established, and every case of cancer was included. Since our object is to induce regression in all cancer patients, each case should be recorded as completely as possible. Family history, personal and social habits, diet, past medical history, allergies, travel, and occupational environment should be included in every history. It has been said that in detective work, sometimes the least suspected set of circumstances yields the culprit. To find the common denominator of S. R. is a supreme test of such a maxim. Unless medical detectives follow these prerequisites, and unless clinicians provide adequate and complete files, the phenomenon of S. R. of malignant disease will remain nature's secret.

## SUMMARY

1. In the introduction, definitions and criteria are given. Clinical evidence of spontaneous regression of cancer is categorized.
2. Twenty-one cases of reports of spontaneous regression occurring in the literature are listed. They are provided solely as examples used in discussing possible factors in regression. It is not implied that all cases of spontaneous regression given in medical literature are listed.
3. In the discussion, several possible factors responsible for spontaneous Regression are suggested. Those factors include: endocrine influences or production, unusual sensitivity to inadequate radiation or other therapy, fever and/or infection, allergic or immune reactions, interference with nutrition of the tumor, and removal of the carcinogenic agent. The significance of evidence of spontaneous regression is discussed.
4. It is concluded that unless more complete and thorough cancer registries are created, and unless more complete histories are provided by clinicians, the common denominator may continue to allude medical science.

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