Progress in

CLINICAL CANCER

Volume IV

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Edited by

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Foreword

New developments are constantly occurring in the over-all attack upon cancer. Volume IV presents some of them, with an attempt to emphasize the newer technics being developed for earlier diagnosis of cancer. The volume commences with a section dealing with general considerations in the over-all attack upon cancer. An exciting lead chapter by Dr. Kenneth W. Starr demonstrates the influence of the cellular environment upon neoplasms and the possible relationship between human ontogeny and human oncology. Then follow chapters dealing with organizational and incidence data. A description of the International Union Against Cancer places in perspective the great accomplishments of this foremost organization. The over-all incidence and mortality from cancer in the United States and the effect of ethnic background, as related to the incidence of different cancers as observed in Hawaii, are next presented.

The question of cancer cells in the blood is an important one, and Dr. Karpas and Dr. Madden present evidence demonstrating that many cells, believed in the past to have been cancer in the blood, are actually megakaryocytes.

Increased information is constantly being gained regarding the interrelationship between the lymph system and the blood system and their relationship to cancer dissemination. This is described in depth, as is the ability (or inability) of the lymph nodes to function as a barrier for tumor dissemination.

The laser beam in its relationship to cancer is described. Next, the exciting studies by Dr. Cronkite, regarding extracorporeal irradiation, are discussed; this chapter presents the effects of extracorporeal irradiation upon lymphopoiesis, a technic with multiple wide-reaching possibilities.

The second section deals with diagnosis; it is in this realm that the great advances in the immediate future are to be expected. Surgeons and radiologists have long realized that superradical surgery or heroic irradiation seldom has great ability to cure far-advanced cancer. The control of cancer depends upon earlier diagnosis. Various technics which have developed regarding earlier diagnosis are discussed. The differential diagnosis of tumor of the neck and the preoperative localization of parathyroid tumors by scanning technics are discussed. The ability to diagnose aldosterone-producing adenomas by adrenal vein catheterization and the detection of cancer cells in the bone marrow are critically evaluated. The present role of cytology in cancer detection and diagnosis is discussed in detail. Attention is directed to the existence of pathologic states in the endocervix, and the exciting studies of colposcopic exploration of this region are discussed by the pioneers of this technic.

Inasmuch as lung cancer plays such an important role in the over-all problem of human oncology, two chapters present the current accomplishments in the control of bronchogenic cancer.

The biologic effects of irradiation have long been investigated, and their possible carcinogenic hazards are presented.

The role of radiation therapy in the primary treatment of patients with breast can-

cer is discussed by experts who have had tremendous experience and have devoted years of study to this particular problem.

The present role of radiation therapy in the management of esophageal cancer and the effects of radiation therapy on the lymphatic vessels and the lymph nodes are next presented.

Newer technics of internal irradiation are discussed in two chapters; the first, dealing with radiating resin microspheres, presents the accomplishments of administering radiation sources intravascularly for their eventual localizations in cancer, and the last chapter of this section presents the effects of giving, endolymphatically, radioactive isotopes for the over-all management of malignant lymphomas.

The last section of the volume deals with certain specific neoplasms. The problem of recurrent endometrial carcinoma and the accomplishments in treatment of these recurrent cancers are clinically evaluated.

The accomplishments of combined irradiation and surgery for cancer of the thoracic esophagus are presented. The ability to diagnose breast cancer in its presymptomatic stage is emphasized by Dr. Henry Patrick Leis, a pioneer in the development of screening technics for the detection of the subclinical cancers of the breast.

An exciting chapter dealing with neonatal neuroblastoma, which stimulates the curiosity regarding the development of a cancer essentially in utero, is presented by Dr. Becker, Dr. Schneider, and Dr. Krasna.

The last chapter presents the effects of estrogen therapy for prostatic cancer and demonstrates that, whereas marked palliation can be obtained in patients with extensive prostatic cancer by the administration of estrogen, the life span is not prolonged because of complicating vascular reactions.

It is the editor's fervent hope that these presentations will alert the clinician regarding newer technics available to him for diagnosing earlier and treating certain cancers, and will stimulate others into developing further methods for earlier detection and the best treatment modalities available today for any given patient suffering from cancer.

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Contents

Growth and New Growth: Environmental Carcinogens in the Process of Human Ontogeny

KENNETH W. STARR, F.R.A.C.S.

Organismic phenomena should be studied as such, and not deduced from molecular phenomena. Man is an organism, not a molecule. Mankind is a remarkable Mendelian population of a remarkable sort.—T. Dobzhansky, 1963.

INTRODUCTION

In 1775, Percivall Pott of St. Bartholomew's Hospital, London, published his *Chirurgical Observations*, and drew attention to the soot warts preceding chimney sweeper's cancer. He thus laid the foundations of the modern disciplines of *experimental carcinogenesis*, and of *geographic pathology*. It is now contended that 70 per cent of human cancer is caused by environmental carcinogens, but the benefit to the cancer patient arising from this approach has yet to be demonstrated.

Pott's second observation on chimney sweeper's cancer is less well known, but may yet turn out to be the more important. "I never saw it," he wrote, "under the age of puberty. . . ." He thus established, for the first time, that relationship between environmental carcinogens and the process of human ontogeny which is the main theme of this chapter. In this manner, the problem of human cancer was elevated from the molecular to the organismic level. The emphasis is not, then, on the laboratory investigations of the cancer cell and its organelles in vitro, but on the pathologic physiology of the cancer patient.

These differences are even more stupendous when that organism is *Homo sapiens*. The evolution of his homoeostatic capacities is only made possible by the concurrent organization of a central, an automatic, and an indispensable neuroendocrine system. This experiment of Nature has required hundreds of millions of years. "It is well to remember," writes French, "that all living organisms from Amoeba to Man are single units, and not just collections of systems. Irrespective of their station in the phylogenetic scale, they must react to the surrounding environment, if they are to survive."[11]

REACTION OF ORGANISM TO ENVIRONMENT

The capacity of an organism to react to the challenges of a changing environment is an inherent property of living matter, and is expressed as an incessant motion in space and time. From this sensitivity to external influences, living structures develop a natural periodicity—a biological rhythm—often related to light and dark. This periodicity is fundamental to many body activities, and such rhythms are evident in, and consequently subtend, the ontogenetic sequences of the life cycle. The concatenation of these rhythms in man produces the great epochs of human development, with which all are familiar—infancy and childhood, puberty, adolescence, reproductive maturity, menopause, senescence, and death at the end of the life span. The more important epochs in human ontogeny are puberty and the menopause. "The onset of puberty is delayed well beyond the time when the pituitary gland and the gonads are ready and capable of functioning in adult fashion. Studies on experimentally induced precocious puberty indicate that puberty and its timing are the concern of the brain. The brain, however, does not act autonomously in this regard, but, in turn, is subject to environmental and hormonal influences, especially gonadotrophic, which interact in several ways to determine the event."[7] There is evidence that both active promotion and inhibition

THE

CHIRURGICAL WORKS

OF

PERCIVALL POTT, F. R. S.

AND

SURGEON to St. BARTHOLOMEW's HOSPITAL.

A certis potius et exploratis petendum esse præsidium; id est, his quæ Experientia in ipsis curationibus docuerit; sicut in cæteris omnibus artibus: nam ne Agricolam quidem aut Gubernatorem Disputatione, sed Usu fieri.

A. CORN. CELSUS.

LONDON:

Printed for HAWES, W. CLARKE, and R. COLLINS, in Pater-noſter Row.

M DCC LXXV.

CANCER SCROTI.

RAMAZINI has written a book de morbis artificum; the Colic of Poictou is a well-known diſtemper; and every body is acquainted with the diſorders to which painters, plummers, glaziers, and the workers in white lead, are liable: but there is a diſeaſe as peculiar to a certain ſet of people, which has not, at leaſt to my knowledge, been publickly noticed; I mean the chimney-ſweepers' cancer.

It is a diſeaſe which always makes its firſt attack on, and its firſt appearance in, the inferior part of the ſcrotum; where it produces a ſuperficial, painful, ragged, ill-looking ſore, with hard and riſing edges: the trade call it the ſoot-wart. I never ſaw it under the age of puberty, which is, I ſuppoſe, one reaſon, why it is generally taken, both by

Plate I. Frontispiece and page 734 of *Chirurgical Observations*, by Per ivall Pott, London, 1775. (Courtesy of the Cowlishaw Collection of the Royal Australasian College of Surgeons.)

participate, depending upon the degree of organization of the nervous system.[7]

Each cancer in man has a distinctive frequency and age of incidence in each population. This age incidence shows either a peak or a plateau. When graphed, these peaks show a relation to the various epochs of ontogeny. This association of human cancer with the ontogeny of the human life cycle is not widely emphasized, but the "seven ages of man" are afflicted with their own cancers, which are distinctive and cannot be confused with those of other epochs. In any study of human cancer, therefore, consideration must be accorded to the biological rhythms, and to their control and coordination by the brain (Fig. 1).

Ectomorphism and Male Cancer

In order to study the differences between cancerous and noncancerous patients, groups of individuals, each of the order of a centile, 50 males and 50 females, suffering from proved cancers of known pathology and fate were investigated.

My colleagues, Freedman and Chorlton,[10] made a detailed study of the anthropometry of such a series of cancer patients and controls, and the data were prepared for computer analysis. This study was combind with a general physical assessment according to accepted standards of health, and with anthropometric evaluation by the Sheldon method. They reported as follows:

1. There was no single character for which a significant difference existed between cancer and control populations, when both sexes were considered together.

2. *Male patients* showed significant differences for: (a) *ponderal index* $\left(\text{height}/\sqrt[3]{\text{weight}}\right)$, $p < 0.001$, and (b) *handedness* (left > right), $p < 0.05$.

3. *Sex differences* between cancer and control groups show: (a) *Cancer group:* ponderal index, $p < 0.001$; skin color, $p < 0.01$; and hair graying, $p < 0.05$. (b) *Control group:* cerebrovascular disease, $p < 0.05$; and hair eolor, $p < 0.05$.

The cancerous male therefore, compared with selected controls, was of a lighter build and taller. Such an increase of linear height is one of the features of the action of growth hormone (HGH, STH) especially during the period of the adolescent spurt. A marked effect of the environmental temperature is manifest (Fig. 2), so that this phenomenon is more marked in the summer months.

Eveleth,[8] reporting upon her observations of the children of temperate zone parents growing up in the tropics (Rio de Janeiro), remarked upon the results of heat stress during the growing period. She found that these children manifested morphological and physiologic differences from the corresponding populations of temperate zones. They were more ectomorphic, less stocky, less heavy, of greater height, and longer calf length, with earlier menarche and second dentition. In fact, these are the changes associated with acclimization to heat stress, providing a physique best adapted to hot climates, and accordingly most commonly encountered among tropical peoples.

It was assumed, therefore, that the higher environmental temperature acted upon the thermoregulatory mechanism of the hypothalamus (supraoptic and mammillary nuclei) to stimulate increased secretion of STH.

There is a notable resemblance in these findings to those found by my colleague, Dr. A. Freedman, who personally examined, in a detailed clinical and anthropometric survey using the Sheldon scale, 100 patients and controls. He reported as follows:

1. *Male cancer patients* have significantly *higher ectodermal score* than male controls, i.e., *ectomorphism* ($p < 0.01$).

2. *Male cancer patients* have a significantly *lower mesodermal score than male controls, i.e., less mesomorphism* ($p < 0.02$).

3. *Male cancer patients* have a significantly *lower endodermal score* than male controls, i.e., *less endomorphism* ($p < 0.05$).

4. *Male cancer patients* have a significantly *lower endodermal score* than *female cancer patients,* i.e., *less endomorphism* ($p < 0.05$).

GROWTH HORMONES

This anthropometric ectomorphism directed attention to the increase in linearity resulting

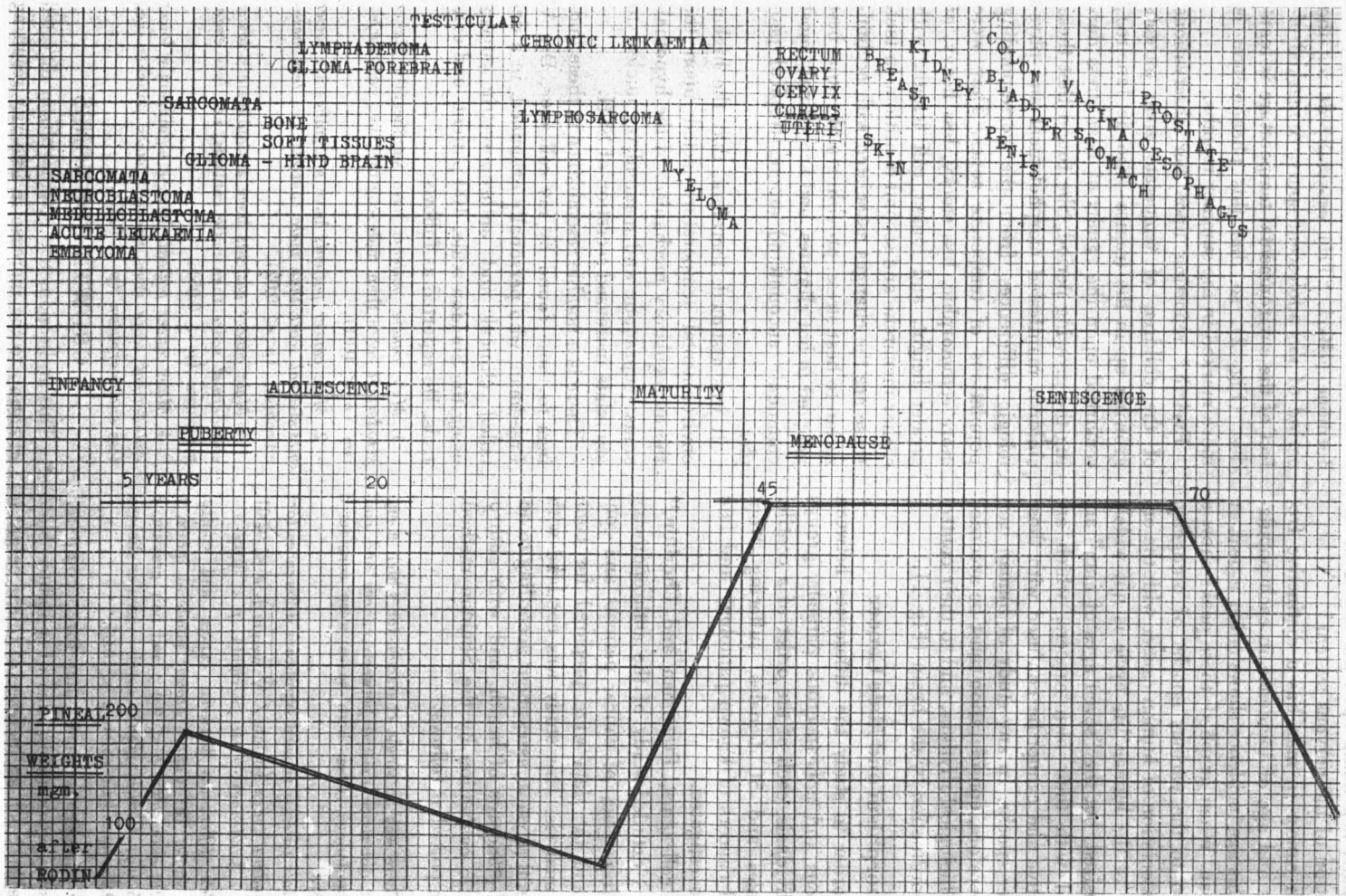

Fig. 1. Human ontogeny compared with the peak incidence of various cancers. Data from Harnett.[12]

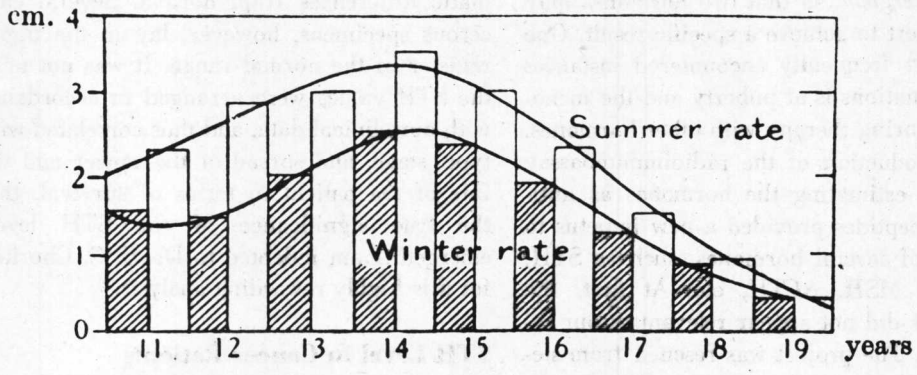

Fig. 2. Rate of seasonal growth in German recruits during adolescent spurt. After Thompson.[32] (See also Lee, J. A. H.: *In:* Ariel, I. M., Ed.: Progress in Clinical Cancer, Vol. III. New York, Grune & Stratton, 1967, p. 96.)

from the exhibition of growth hormone. First, the chemical composition of various HGH molecules was examined. The electrophoretograms of normal, standard (Australian CSIRO), and cancerous sera were compared, and no evident difference was recorded by my colleague, Mr. J. B. Adams (Fig. 3).

The growth hormone (*HGH, STH, somatotrophin*) and its close relatives HPL (human placental lactogen) and human prolactin are in close association with the human individual from the uterus to the grave, being measurable in the serum from the third to the ninety-first year. The hormone has other important actions besides growth (calcium absorption from the gut, fatty acid mobilization) not directly related to the increase of body mass and height. This hormone acts at cellular level and does not appear to be under hypothalamic control. It is for these reasons that it is preferred to term it somatotrophin (STH) rather than growth (HGH) hormone. Depending upon the tissue concerned, modification of the metabolism is effected in many diverse ways not all related to the phenomenon of growth. Nor is it clear whether a single primary action or multiple primary actions are required to effect its several different results. The active amino acid sequence varies from species to species, but there are greater similarities than at first believed. All, however, have the fundamental role of increasing, in favorable circumstances of nutrition and hormone development, the protoplasmic mass by the retention of nitrogen, and those electrolytes required for anabolism.

Depending upon the hormonal state of the host, STH, like many hormones, shows *ambivalence*, with excitatory effects upon one tissue and inhibitory influences upon another, as

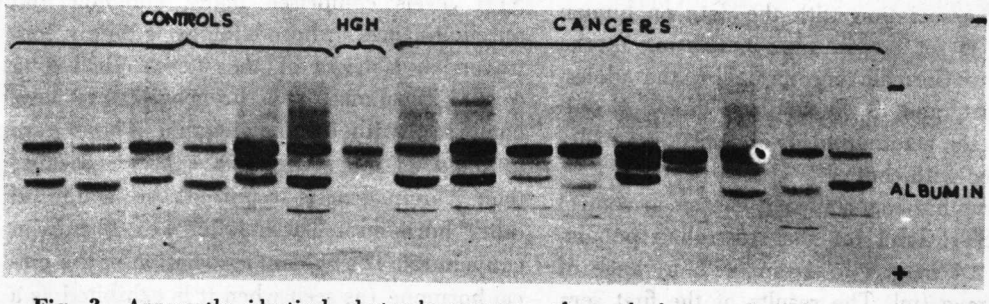

Fig. 3. Apparently identical electrophoretograms of standard, normal, and cancerous sera for STH.

well as *synergism*, so that two hormones may act in concert to achieve a specific result. One of the most frequently encountered instances of these situations is at puberty and the menopause, or during therapy with other hormones.

The introduction of the radioimmunoassay method of estimating the hormones as antigenic polypeptides provided a new impetus to the study of several hormones, such as STH, LH, FSH, MSH, ACTH, etc. At first, the STH results did not appear relevant to our investigation. The project was rescued from sterility by the association or our clinical data with the results of the STH assays. These estimations were carried out by Dr. Lazarus, Director of the Garvan Institute of Research, at St. Vincent's Hospital, Sydney, Australia. He has described his methods with particular reference to the problems of pediatric growth.[20]

Seasonal Variation of Human Cancer

The anthropometric data provided by our survey of cancerous patients compared with controls was reinforced by the reports of seasonal variations in the incidence of certain human cancers from reliable sources in the United Kingdom. (See *Progress in Clinical Cancer*, Vol. III.) Price reported the variations in the case of osteogenic sarcoma,[25] Cridland the seasonal variations in lymphadenoma,[6] and Lea the seasonal variations in mammary carcinoma.[21] In all instances, the higher incidence occurred in the summer months.

This correlation of human cancers and their frequency with seasonal variations provided a striking association with the data on human growth as set out in Fig. 2, relating to the growth of German recruits during the adolescent spurt, and to the findings of Dr. Freedman on the ectomorphism of cancerous males compared with controls.

Lazarus has reported that the mean control serum STH level for the Australian population is 2.4 mμg./ml. serum, with a range of 0.4-7.7 mμg./ml. The results of the first sera examined indicated that there were no dramatic differences from normal. Several cancerous specimens, however, lay in the upper register of the normal range. It was not until the STH values were arranged in accordance with our clinical data, and thus correlated with type, stage, and spread of the cancer and the fate of the patient in terms of survival, that the true significance of the STH levels emerged. I am indebted to Dr. S. C. Chorlton for this highly rewarding analysis.[10]

STH Level in Cancer Patients

The first revelation was that the STH levels were not uniform in the various cancer groups, the highest readings in the cancerous sera being related to the multiplicity of the primary cancers, while those in the sarcomata of the soft tissues and bones were to be found next with the gliomata and the cancers of the colon (mainly sigmoid). (See Fig. 4.) The readings thus varied without any basic pattern until the clinically orientated classification was adopted. The surprising result of the exercise then became apparent. The cancers studied by us fell into two major groups depending on the STH levels in the serum: (1) those with high STH readings, and (2) those with low STH readings.

The first group included sarcomata of the soft tissues and bones, the cancers of the sigmoid colon, the gliomata, and certain reticuloses (chiefly composed of lymphadenoma and chronic leukemia.) These cancers with the high STH levels were termed *somatotrophic cancers*.

The second group with predominantly low STH levels comprised many common and puzzling cancers whose etiology is highly controversial. Cancers of the uterus (including cervix), mamma, and bronchus were here comprised with the melanomata. These were grouped as the synergistic cancers, because their carcinogenesis required the action of other hormones. These latter are at present conjectural. The evident association of the pineal hormone (as seen when it is exhibited as a prelude to perfusion for melanoma) with the

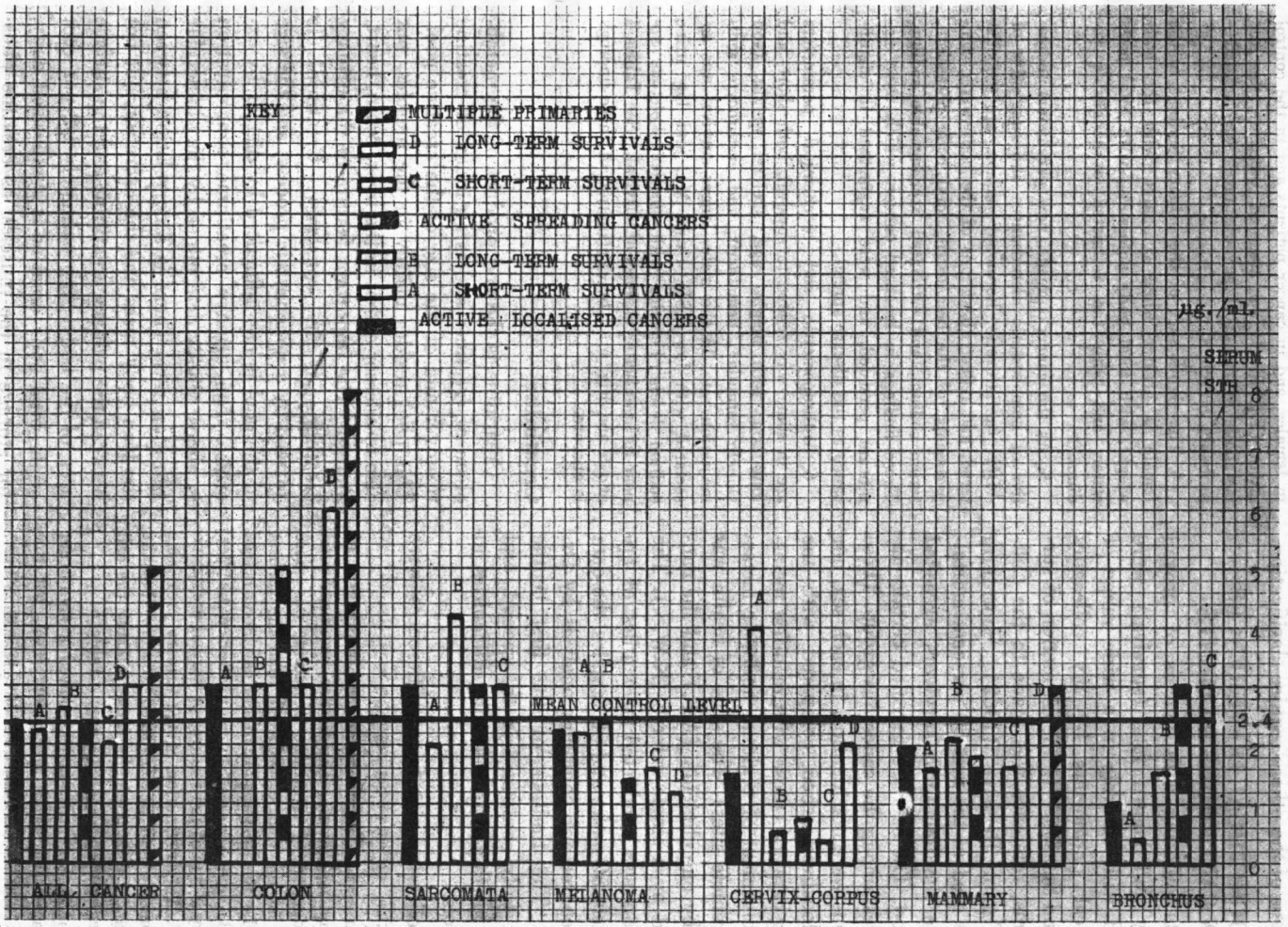

Fig. 4. Serum somatotrophin levels in various cancers: active localized, active spreading, and survivals.