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Toxemias in malignancies

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TOXEMIAS IN MALIGNANCIES

by

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INTRODUCTION

Aside from the rapidly growing tumor mass and possible metastatic growths, nothing strikes the individual interested in cancer as being outstandingly persistent in all types of advanced internal malignancies as the profound cachexia, the malaise, cerebral depression, anemia, anorexia, weakness and general debility which accompanies the proliferation of tissue cells. Despite such observations which occur in cancer, little thought beyond casual mention of its presence has found its way into the literature. To the best knowledge of the author, this is the first discussion of the toxemias in malignancies per sé.

The specific toxin has never been demonstrated to exist concurrently and elaborated directly from the malignant tissue. Some writers claim it exists. Many believe toxins are produced by incidental invasion of the tumor. Others think toxic products result indirectly, from altered metabolism due to the presence of the mass. Still other authors predicate the existence of materials in the body due to the rapidly growing, degenerating, and destroying infiltrative tissue. However, practically all observers permit the supposition that toxins exist and casually speak of it in clinical work and make note of it in laboratory reports.

This author attempts to collect such clinical and laboratory data that will point toward the presence of toxemias in carcinoma and sarcoma. Such changes from the normal either by the advent of new and unusual substances in quality and the increase
or decrease of usual materials in quantity are noted here if they seem to indicate toxic products in the blood stream. Likewise, such diagnostic procedures based on these changes or on the incoming constituents have been briefly summarized. The nature and source of toxic products have been discussed as well as several lines of treatment for the general condition. Mention of etiology and pathology of cancer has been conspicuously omitted as was the progress of the local manifestations of the disease. Because such toxemias have not been isolated nor positively detected, it is only possible here to note their effects as seen in clinics, laboratories and experimentally.

Similarly, in that the type of toxemia and its results are unknown, they must be compared to toxemias which are clinically proven and laboratory tested. These include toxemias of pregnancy (2), of bacterial invasion, of gastro-intestinal autointoxication, of thyroid toxicosis, sinus thrombosis, animal poisoning, and parasitic invasion. Whether of primary origin or indirectly to tumor metabolism, or due to necrosis with split proteins jettisoned off into the blood stream, or to secondary bacterial incursion, the author attempts to deal only with evidences of toxemias. This does not purport to be a comprehensive or exhaustive study but a resume of most of the facts that lead to the correct supposition that toxemias, whatever their source, exist.
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DEFINITIONS

A. Toxemia

Briefly stated, by toxemias it is meant toxins in the blood stream. Dorland (43) defines toxemia as 'a general intoxication due to the absorption of bacterial products formed at a local source of infection.' Toxocosis is defined as any diseased condition due to poisoning and the types are endogenous, an autointoxication, and exogenous, a poisoning due to ingestion of toxic material as from foods, and thirdly, a retention toxicosis which results from non-excretion of noxious waste products. Toxins are 'any poisonous albumin produced by bacterial action'. It is well to note that Webster defines a toxin as any of a class of unstable, toxic substances formed as secretion products of a vegetable or animal organisms.

Such definitions as given for toxins, toxemias, intoxications and toxicosis are for the purpose of this thesis not strictly tenable except for Webster's explanation. Bacterial and proteic toxins are not all the types of toxins that exist. There are toxins from altered metabolism, from septic thrombosis, those with thrombosed infarcted areas, those in pregnancy, from gastro-intestinal autointoxication, in the thyroid toxicosis, which do not conform with the category of the stricter definitions above. Likewise suspicion of toxemias are manifested by clinical symptoms and qualitative and quantitative changes in the blood stream.

In a broad sense then, are toxemias described below, to be existent. Vaughan and Novy (3) classify cellular toxins as being bacterial, protozoal, fungus, animal parasitic, intoxications traumatic and autogenous. Toxins are not always to be considered
proteic or albuminous in nature but it is assumable that they are any deleterious or obnoxious material whose action is felt systemically and effects felt locally at site of liberation. The extent depends upon the amounts exuded and the site or the organ involved. Because with the liberation of toxins, the usual mode of spread is via the blood stream, the term toxemias is used in that all toxins no matter what the source finally reach the blood system. That it exists at all, must be interpreted from the data that is collected from the literature as indicated below. Thus, by toxemia, it is included any normally present substances unusually large amounts as to become deleterious. Toxemias are then, obnoxious substances in the blood stream. Because there are likely more than one toxin present, the plural, toxemias, is used.

B. MALIGNANCIES

By malignancy, it is meant a tumor—a new growth of a new cell (40)—, a neoplasm which has certain features that distinguish it from benign or innocent tissues. These are (4): invasion of surrounding structures, recurrence after partial removal, production of metastases and lastly cause of cachexia. It is with this latter feature that we are most concerned. Ewing (40) says another differentiation is in the general 'toxic action of absorb tumor products'.

The term malignancies has been used to include carcinoma and sarcoma. About 75% of all tumors are mesoblastic in origin of which 5% are malignant and 95% are benign. The remaining 25% are epiblastic in which 95% are malignant and 5% are benign (4). Therefore most of the discussion deals with carcinoma, the epithelial type of malignancy... Sarcoma and carcinoma as far as toxemias are concerned are fundamentally alike in elaborating the toxins.
Janeway cites Piscateri's case in which at autopsy a carcinoma of the breast and one of the pylorus were of different histological structure. Again, the fundamental identity of the two is indicated in that fat soluble substances can stimulate either carcinoma or sarcoma (11). Sarcoma and carcinoma may occur simultaneously as reported in a case of renal osteogenic sarcoma and breast carcinoma (adenocarcinoma) in a guinea pig (6). While carcinoma occurs generally in more advanced ages and sarcoma in younger, when carcinoma does occur in young individuals it is more toxic in effects and in the progress of the disease than it usually is in the older individuals. Thus the latter is more resistant to the Carcinoma although its incidence is quite high. Therefore, the sarcoma progresses more rapidly than carcinomas correspondingly, both are due to the decrease in resistance of the young patient to the malignant growth.
II. NATURE AND SOURCES

Of the nature of such toxemias that may be elaborated in malignancies, only surmises can be made. It is not likely as entirely bacterial, or to altered metabolism, or influence of chemical factors, or to split proteins, or enzymal action or to unusual mineral products present but its best to consider the toxemias as the composite result of the above. The process may be the cause of extent of the findings dwelt upon in subsequent description. It is not far fetched to assume that toxins once elaborated, may be the further cause of advancement and local encroachment of tissue, and the debilitation of systemic intrusion.

Quigley (4) and other observers claim that 'the living cell, itself, contains no poison and produces no poison but the dead and dying carcass produce the poison of the cancer according to the kind of microorganisms acting on it.' If the organ can overcome the active virulence of the infectious organisms that may be the source of the toxins occurring with malignancy, it would explain the cases of spontaneous recession which practitioners report (8)(41). Vaughan and Novy (3) believe that toxins are produced from bacteria either by a soluble chemical ferment or that microorganisms act directly and indirectly to split up complex proteids in producing among these split products, the specific poisons which induce the characteristic symptoms of the disease and leads to death. Secondly, that the bacterial toxins are synthetical rather than analytical. The toxin is a constituent of protoplasm and its formation a vital phenomena of cell life. These poisons, they continue, act first on the immediate tissue, then get into the blood stream to act systemically.
Of the nature of the toxins, Roux and Yersin (3) thought it might be a ferment. Breiger and Fraenkel thought the diphtheria poison was a albuminous body. Isolation of toxins were difficult, Frier and later workers never found Sulfur as being present in any toxic material they isolated. Uschinsky (12) proved that toxins are synthetical and not formed from proteids in culture in which the bacteria grew, for the media was free from any protein matter. Its composite is not known tho tar cancers produced experimentally yielded deleterious substances as beta-naphthylamine and amiline (9). Schwerin (10) reports benzidin and fuchsin present.

That toxins may be elaborated from bacterial sources is believed by Quigley (4) who says that bacteria are present as irritation factors in cancer development and toxins come from bacteria already present and those secondarily attracted to the site of ulceration, necrosis and disintegration. Wells (12) says that since tumor tissues are being disintegrated all the time, enough products of autolysis get into the blood stream to cause protein fever and toxic systemic disturbance associated with malignancies. In extensive necrosis of the experiments with rat and mice tumors, animals show profound toxemia presumably because of absorption of autolytic products. Boveri and Kline (36) explain the nature of cancer as the change from benign to malignant tumors by the action of toxins and like substances on the chromosomes to alter the same.

That toxemias may be the result of altered metabolism
is suggested by Wells (12) in that tissue cells elaborate metabolic products in sufficient quantities to cause disturbances in the body. Kullmann (13) has demonstrated ptomaines and like substances from the urine of cancer patients. Phenol and indican and oxyacids are said to occur in the abnormal metabolism of the tumor proteins. In rats with sarcoma, increased excretion of uric acid and creatine was observed by Ordway (14). Metabolism in cancer resembles fever and warrants the assumption that toxic stimulation of tissue destruction and these products of protein destruction in cancer, says Vaughan (3), cause the toxicoegenic metabolic abnormality because the effects of foreign proteins are the same in their pyretic action. In analyzing fibroid degenerations into malignancies, it was found that the degree depended on the degenerations (15).

That the subsequent illustrations of physico-chemical changes relate to toxemias is evident in that tissue fluids may inhibit the growth of noxious agents or permit of their dissemination for Fischer says the composition of the medium has an important quantitative effect on the growth of the cells. Increased proliferation of cells is due to excessive absorption of a chemical agent which makes cells divide by a reduced number of chromosomes in carcinoma cells and eosinophilic leucocytes (17). This chemical agent may be the toxin.

Epithelial cells were shown to respond to chemical exciters. Products of katabolism contain causes of cell reproduction for carcinoma cells will develop best where areas of putrefaction and dead tissues are numerous in amount (17). Ross says cancer is
unknown amongst esquimoes because the air is lacking putrefactive organism. Cancer, he continues, is due to the physiological auxetics combined with the pathological alkaloids of putrefaction. The latter are considered as break down products which are toxic by the nature of their activity.

That a virus may be the cause of the toxemia is advanced by the workers with the Rous fowl sarcoma (18). Gye and Purdy believe this virus is elaborated by parasitic infection and cause the general toxemia that results. Their theory supposes a specific and a non-specific (the virus) factor as the cause of cell growth, multiplication and general systemic symptoms of cancer.

That the tumor itself is capable of elaborating protein products which become toxic is proven by the extraction of a substance from human cancer which is severely toxic to mice by Seyerderhelm and Lampe. Mertens confirmed this. Eggers in summarizing these experiments offers the conclusion that toxicity may result from the partial protein cleavage products (19). The nucleoprotein group was found to be toxic in that they could stimulate excessive mitosis even in relatively fixed tumors with changes, as Calkins, Bullock and Rohdenburg noted in 1912, to make it appear precancerous. It was reasoned that if local autolytic products were released, latent cells would be stimulated to divide rapidly (19).

Little work has thrown light on the possibility of exogenous toxic products being liberated from the cancer cell itself. Quigley and Wood do not grant the likelihood. In 1903, Clowes (19) altho favoring the parastic theory in the etiology of cancer, did acknowledge the possibility of stimulant toxins formed within the cell. Many observers favor the necrohormone theory of dead or degenerating cells stimulating cell growth. In 1910, Stoebner and Wells
used split protein products to cause toxic symptoms in rabbits. In 1912, Ross found that leucocytes exposed to extracts of dead and dying tissues, themselves underwent rapid division. The auxetics usually contained the amidine radical. Calkins, Drew, Eastwood, Meyers and Wright were inclined to the belief that necrohormones caused cancer (19). Notwithstanding their premises, the split proteins clinically and experimentally were shown as the basis for toxicity irregardless as to the possibility of it being the cause of cancer.

In an unusual original publication, Marshall (20) claims that toxins arising from the disintegration of cells of the chorial villi by carcinomatous and sarcomatous processes are definitely present. He claims the cancer cell and toxin derived from it as being due to combination of leucin (in carcinoma, sarcoma and yellow atrophy of the liver) and the formation of ferric oxide with the aid of several oxidizing intracellular enzymes.

Probably the only direct surmise as the source of a toxin from the carcinoma cell itself is found in Pericaud's (21) explanation that the cancer toxin has an epithelial origin just as snake venom. He claims for a cancer poison analogous to snake venom tho it is not as lethal. There is a metabolic intracellular source for a neurotoxin and hemolysin. The cachexia, he goes on, is due to toxic lecithins in cancer. It was found (22) that erythrocytes of cancer patients have a greater resistance to cobra venom than normal persons and that stomach contents in ulcerated gastric cancer are hemolytic. Quensel's work (28) in autopsy specimens of cancer blood where metastases had occurred, cancer cells in the
blood indicated to him that many of these cancer cells are destroyed and their products contribute to the cachexia. It infers that cachexia is due to something released from the cell itself with the hemolysis. This implies an endogenous basis for cancer toxemias. Likewise intracellular metabolism may be important in the elaboration of toxins for Kluyver (23) states that a large part of the food constituents leave the cell again after undergoing profound chemical alteration. In cancer, the conversion of a normal cell into cancer would depend on the qualitative change in the property of a catalytic agent.

That microbes are definitely related to cancer and toxemias is shown by Quigley (24) quoting his own and the Memorial Hospital figures wherein 50 to 90% of the patients having Cancer of the tongue had positive Wassermanns. This indicates that the toxemias resulting so frequently here, may be associated with the incidence of the spirochaete in the oral cavity. Tuberculosis is related similarly for the acid fast bacilli as a source of irritation, may aid in generalized symptoms seen in cancer. The fact that organisms may be present and remain undetected is proven by positive Von pirquet reactions. Likewise Mori reports cultures of microorganisms resembling those of Creatina, Coronia and others, which he obtained from eleven deep seated cancers of the breast. They may be the traumatic agents associated with etiology and toxin formation in cancer. The entire picture may explain the lymphocytic reaction occurring in and around the cancer tissue. This does not take part in defense but does to the infectious agents lurking in the region (25). It confirms Quigley's contention that there
are bacteria and saprophytes in every malignancy, dormant (33). Finucci (32) found that latent bacterial flora of saprophytic organisms were present before and after malignant disease was demonstrated present. Sokoloff (26) claims that the leucocytic reaction may be the cause for malignant invasion of tissues. He says leucocytolysins are present, and explains the diminished lymphocytosis in the presence of an increased polymorphonucleosis.

Support to chemical basis for toxemias is given by E.P. Robinson (29) who noted that the absorption of toxic products plus irritation in the physiological hyperplasia and hypertrophy of certain parts causes the increased proliferation of cellular elements. Given substances may be slightly altered in its chemical constituents to become toxic just as benign tumors are merely stages in malignant growth, despite Broder's classifications.

Muller has a theory that there is a specific toxogenous disintegration of protein in cancer (30). This disintegration of protoplasm that causes toxicity is independent of nutrition, says Round (30). The cachexia accompanying cancer is a generalized affair resulting from cancer said Sir Wilks after autopsies (2000), at Guy's Hospital and the anemia is due to specific effects of the hypothetical cancer toxin.

Meyer (31) offers evidence that substances described by Menetrier are degenerated tissues on which autolytic processes act that transform them into substances that are different. It is produced by decomposition of cell proteins, into amino acids. Enzymes in malignant tumors split the protein molecule into amino acids to form a specific toxic proteids, claims Sivori (34).
in tests for cancer. Marchand, in 1902, believed that in certain conditions, elements that were toxic, became liberated to stimulate new growths. Experiments by Walker in the injections of protein products of cleavage, pyridine, indol and skatol growths and its accompanying manifestations occurred, in rabbits. Leucocytic infiltration preceded epithelial proliferation to indicate a condition similar to inflammation or reaction to bacterial and toxic invasion. Glover (35) claimed the discovery of a pleomorphic organism causing cancer and its toxemia. That carcinoma may occur simultaneously with tuberculosis is shown by Thibeudeau (37) in a series of 21 cases where both were demonstrable.

Tho Ewing (38) states that cancer itself exerts no toxic action yet its end products are anemia, infection, mechanical obstruction and an auto-intoxication of an acid nature from the degenerating tumor. E.P. Glover describes the lytic action of normal serum over cancer serum, claiming the substance so destroying cancer cells is a dibasic saturated fatty acid with a molecular weight over 300 that combines with the nucleoglobulin of serum. Its toxic action on cancer cells accounts for the deficiency of cancer serum to overcome the new cytolytic, destroying agent found in cancer tissue.

Perhaps the first work on toxins in cancer was done by Peyrilhe (40) in the late 18th century. He dealt with the cancer toxin, the nature of the disease, the manner of growth and treatment. He mentioned the local growth and the production of a virus from tumor degeneration with the development of cachexia herein.
Muller and Klemperer showed that there was a toxic destruction of proteins in cancer with excessive Nitrogen loss. It was Petry who showed the rapid autolysis of tumor tissue was due to autolytic ferments as the source of the existent toxemias. Neuberg, Jacoby, Wolff and Blumenthal claimed for a heterolytic action of tumor ferments (40).

Of the nature of toxemia little is known. Of the source, it is to be concluded, there are many. It may be from the cancer cell itself either endogenously or exogenously, or from altered intracellular metabolism, or from intracellular enzyme activity. The toxins may result from activity indirectly caused by the tumor presence as in disintegrating tissues with its split protein materials. It may be due to primary bacteria flora and saprophytes in the area or due to secondary microbial invasion with the ulceration and necrosis. It may be a parasitic or spirochaetal cause at times. These may be of minerals and vitamin deficiency relationships to toxemias (45). Toxins are new products, qualitatively or quantitatively and often present, which have been jetted off into the blood stream to cause systemic disturbances along with the local cancerous growth.
III. CLINICAL MANIFESTATIONS

In considering the clinical findings likely due to toxemias in malignant diseases, the author includes discussion of cachexia, weight loss, anemia, malaise, emaciation, fever, vomita and its termination—death. Study of laboratory procedures which are a usual routine of any clinic is undertaken here. They include gastric analysis, blood counts and basal metabolic rate. The majority of the experimental work, the serological study and pathology has been relegated to another chapter on laboratory manifestations. The clinical investigations of toxemias are based on the whole on average findings of internal cancers which have progressed beyond the incipient stage. The average was the rule rather than the unusual.

The cachexia of cancer is probably the most outstanding feature in malignancies. When analyzed it is inconceivable to believe that this characteristic of cancer be the result of anything other than the effect of a general toxemia. Many authors (30) show the existence of a tumor mass situated in an organ or some part fails to produce a cachexia merely by its local presence.

Sir Wilks says the cachexia of cancer is due to a generalized condition. Its effect is more than a local one. It is due to materials formed directly or indirectly from the cancer tissue and is felt throughout the body.

By cachexia, it is meant malnutrition. It is a profound, marked state of constitutional disorder; a general ill health. Dorland defines cancerous cachexia, a distinct entity, as the weak and emaciated condition seen in malignant tumor (43). It is seen
as the dryness of the skin, the anorexia, the malaise and progressive weakness. Some observers note hair changes as loss of hair, peculiar growth of hair in certain parts, and color changes. Others include sweats and psychic depression. Tho this occurs with cancer, all of these do not always appear in all malignancies. That the cachexia is part of the toxemia picture is evident by comparing such changes that occur in cancer with similar toxic conditions, elsewhere. Rivers (44) shows that alimentary toxicosis in children is one of shock, weakness, paleness and dehydration. He based the cause on bacterial invasion and their toxic products. His treatment included the use of calcium. Later, it will be shown that in cancer, there is a hypocalcemia.

It is said that cancer is a concurrent incident in debilitated patients and in the aged. To refute this, cancerous cachexia is shown to occur in the young and attends malignancies persistently. Ewing (40) believes that with ulceration, the connected infection, local suppuration occurs and toxic products are absorbed with hemorrhages so that the combined picture make up cachexias. Toxemia and cachexia, says Brown, are characteristic of the cellular type of carcinoma of the stomach. He assumes the inanition, malnutrition and anemia make up cachexia and is in part caused by toxemia. Holland (42) describes anemia and loss of weight with cachexia, associated with a psychic depression due to toxemia. This occurs in cancer of the intestinal tract, and the toxemia, he says, is demonstrable at some time in the disease. Osler (7) states that in colloid carcinoma of the stomach, much metastases occurs with tendency to ulceration. Altho the extent of the lesion has little
effect on digestion, yet it can produce emaciation and cachexia, which is not due to indigestion. He believes that the anemia and emaciation gives a picture of cachexia caused by toxins liberated at this point. Many cases in which there is no blood in the stool or in the vomitus, and those going to autopsy, show no encroachment on the blood vessels. This indicates toxic action on cells.

In cancer of the peritoneum, the constant sign of carcinoma is emaciation. In malignancies of the liver, which is rarely primary, toxic features are frequent only toward the last. This is explainable by the detoxication function of the liver, being able to take care of small outpourings of toxin until it became too extensive, when it is noted clinically. Likewise in the kidney, progressive emaciation occurs rather late and when it occurs, the course is very rapid as if the resistance finally gave way suddenly. Cancer of the lung and other internal organs always show emaciation. Small and non-metastasizing tumors may cause general symptoms far out of proportion to the size of the tumor. Again there is an indication of toxic action remotely from the local origin or site of tumor growth.

Association of cachexia, and often considered a part of the picture, is the anemia seen in cancer cases. Ewing (40) describes it as a secondary pernicious form with the loss of hemoglobin exceeding the reduction of cells—a low hemoglobin index. He claims the anemia is due to hemorrhage and the absorption of hemolytic agents from ulcerating, infected surfaces and from necrosing areas. Maragliano, Bard, Polk and Kullmann demonstrated the presence of
hemolytic properties in the blood of individuals with cancer (40). That a hemolytic toxin is elaborated from the tumor tissue is believed by Crile (46) and Dietrich (47) and Elsberg, Neuhof and Gust in a study of 187 cases. Eisen (49) thinks a hemolytic toxin is generated from tumor tissue and from its necrosing products. His average figures in 353 cases of cancer were:

- 3,569,000 RBC
- 62% Hemoglobin (Col Idx .88)
- 10,000 WBC; 71% poly-23% lympho.

Hartman (49) suggests the anemia is due to absorption of incompletely digested, toxic, presumably hemolytic split-proteins. Senez (50) offers the clinical demonstration of hemolysis in cancer in a case of hypernephroma with hemolytic agents. Round (30) in England notes the progressive anemia and claims for a specific effect of a hypothetical cancer toxin. Osler (7) states that where the cancer tissues did not encroach on blood vessels and cause hemorrhage, the hemoglobin was unmistakably low. He attributes the onset to a primary anemia which may be from a toxic substance. A low color index in carcinoma cases was noted by Brown (42). Where there is metastases to bone, the color index may be higher (63). Pericaud indicates a hemolytic toxin exists in cancer serum (21).

Leucocytosis is not a distinct and common finding in cancer patients. Louedon in 3 cases of ulcerative cancer with secondary infection found leucocytosis and hyperpolymorphismucleosis. Morrison (52) found the leucocytosis, in over 66% of the 100 cases studied, associated with an assegmentopenia (decrease in band forms). About 99% of the cases showed an eosinophilia (persistence of the
eosin forms in the presence of neutrophilic leucocytosis). There was a leucopenia associated with metastasis in over 50% of cases. Ewing describes leucocytosis being due to ulceration or bacterial infection which locally or generally intensifies the effects of absorption of tissue toxins and loss of blood (40). Its presence in cancer is associated with infectious agents which may be the cause of toxin's liberation. Leszler (83) said neutrophilic leucocytosis was present in many cases of carcinoma and attributed the finding to toxic products from the tumor and to secondary infection of the necrotic growth and the metastasis to lymph and bone marrow.

Basal metabolism is of minor importance yet when compared to elevated figures of thyroid toxicosis, it is seen to occur in cancer similarly. Habell (53) found the BMR in patients with carcinoma of the stomach and intestines raised in 16 out of 19 cases. These patients were free from fever and anemia. He blamed the abnormal destruction of proteins. Narat (54) in a resume of the literature on this subject, concluded the BMR is generally elevated in cancer as in thyroid disease.

Fever is an interesting feature in Cancer. In toxemias, fever is generally present. Campbell (55) says it is fairly common to carcinoma and quotes older writers in their description of "tumor fever". In 173 cases, he found 50% had a fever of 99.0 or above and the highest fevers occurred in cancer of the intestinal tract. The writer said it was due to anaphylaxis but Alexander thinks it is due to auto-intoxication, the toxin acting on the heat regulating
Gordan thinks it is due to absorption of the dead tissue and of the blood in hemorrhage. Stierlin bases it on bacteria. Giodana blames a toxin for he found it present early in malignancy; those coming late are exotoxins and endotoxins of secondary pathogenic bacteria. Geissler believes fever due to ulceration and neoplastic cells causing a reaction in the blood stream while Tizianelli found fever with advanced cases of necrosis. Phillips bases it on constant degeneration of tumor tissue with autolysis, tho Rendu writes that fever is due to the diffusion of toxins elaborated by the tumor.

Skin temperature claims Barelli (56) is higher than normal in malignant neoplasms. The temperature of the tissue itself was found to be generally lower. Briggs (51) notes that fever exists and is prolonged for a long time in uncomplicated cases of cancer. In 25% of the 475 cases at the Zurich clinic (Max Freudweiler) fever was present with complication. Marsh found fever with sarcoma uncomplicated. The commonest type was intermittent (43%) and remittent (10%) of all fever cases of cancer. Metastases had no relation to pyrexia. Wells (12) says that tumor tissues are being disintegrated all the time and its likely that products of autolysis enter the blood stream in quantities sufficient to cause protein fever that explains the toxic systemic disturbances in malignancies. Osler (7) notes that fever is a symptom of cancer and that toxins cause this pyrexia. Because the quantity of toxin liberated may be small, and progressive for a long period of time, the fever is accountably low in early stages and higher later (51). The latter may be explained by late secondary bacterial invasion.

Loss of weight is associated with the general cachexia. This is usually attributed to toxic products in the blood. In cancer, loss of weight is striking even in cases other than intestinal tumors. The
local growth is insufficient to explain the general manifestation. Autolysis is more abundant in malignant tumors than in benign. Holland(42) notes that loss of weight in intestinal cancers are due to toxemias. Since weakness is associated with weight loss, it is a phenomena due to toxic destruction of proteins. This is true particularly when combined with fever.

Friedenwald and Brown(57) state there is a tendency to the production of an achylia and a hypochlorhydria where cancer is not in the stomach or intestinal tract, but in some other organ. Moore believes it is due to an alteration in the blood. This confirms findings below, that there is an alkalescence of the blood. Ewing(40) says that the hypochlorhydria in gastric contents occurred even with new additions experimentally. Moore and Palmer attributed this condition to a reduction in hydrogen ions of the blood.

Coma is a symptom of cancerous toxemia. That it occurs is proven by many authors. Ewing(40) states that in esophageal, hepatic and gastric cancer, v Jaksch, Riess and Senator described a form of cancer coma where low alkalinity of the blood, dyspnoea, and acidosis occurred as in diabetes. Klemperer described a Nitrogen loss of 5-9 grams as a toxic destruction of tissues and the coma due to a general toxic process, not to the acidosis. The coma comes late in malignancy and is often considered an acid intoxication coming on prior to the termination of the malignant disease. Osler advances this thought on gastric carcinoma(7). Gradual weakening pulse, anorexia, inanition and dehydration follows the picture of cachexia. This is a combination of an anemia, emaciation, fever, leucocytosis, and a loss of weight which leads to a termination of coma, and the final stage, death.

The usual mechanism of death in cancer says Blair(58) is not
by starvation, or hemorrhage or pressure but by a toxemia. This is associated with cell proliferation and if leucocytosis is present, believes it is due to bacteria in the urinary tract. Toxemia is the cause of the symptoms usually found before and at the termination of the disease.

That there is an acid intoxication is indicated by the fact that acid areas of the body are more frequently invaded by cancer tissues. Thus, regions that are usually alkaline become acidic. The toxemias, claim most observers, are due to products from within the tumor itself or from the necrosing areas around the tissue. Clinically, toxemias are manifested by their effects. These are not always alike nor always consistently present but they form an integral part of the picture. Sir Gould (59) said 'There is a cure of cancer apart from operative removal!'.
LABORATORY MANIFESTATIONS

A. CHEMICAL AND METABOLIC

The greatest field for collection of indisputable, and newly-discovered facts in cancer research, has been in chemistry. Warburg's work (12) on the metabolism of the cancer cell, regarding the oxidation-reduction and respiratory quotient, has been the greatest advance in the study of cancer. In work on enzymes, much data has been uncovered. Enzymes are forces bringing about chemical reactions. Each cell has an amount of enzymal reaction. They are less affected by poison than its nature—supposed to be proteic—is unknown (12). They affect only organic substances, are specific, and toxic since all foreign proteins are toxic. It is difficult to determine the extent. Hildebrandt (61) found pepsin, invertase, diastase, emulsin, myrosin and rennin all toxic. Action on dogs brought about a terminal coma with fever and hemorrhage being intermittent. This was proven not due to bacteria by Kionka and Achalme. Lombroso determined trypsin an important toxic agent. Noguchi showed that pancreatic lipase once in the blood stream caused hemolysis. Papain was found to be more toxic than any animal enzyme including pancreatin and rennin. Likewise urease was found toxic for it decomposes urea in the blood and tissues, and results in fatal intoxication from Ammonia poisoning. Cobra venom, from epithelial cells, has a lipase which is a hemolytic toxin that splits lecithin into hemolytic substances (60).

Cancer tissues have such enzymes in it which normal tissues do not possess in quality or quantity. The toxicity of malignant tumors is explained by their presence. In cancer, there is an
increased power of the blood serum to inhibit the activity of such toxic enzymes as trypsin and leucocytic proteases. In such toxic conditions as exophthalmic goiter, tuberculosis, and particularly toxemias of pregnancy, it is also seen increased. Enzymes and toxins are alike in that both are readily absorbed by membrane precipitates, and highly developed surfaces. Catalase has no lethal effect on toxins tho liberating oxygen from peroxides, it can destroy a toxin-mixture. In early malignancy this was normal but with cachexia, it was decreased in amount. Bauer (62) in testing surface tension, found human serum has fat-splitting enzymes which are greatly decreased in carcinoma. It is possible that enzymes can both neutralize toxins under proper conditions or act as toxins by not inhibiting toxic activity.

Wells (12) states that when autolysis occurs certain amines are released from the cell (12). Methyl guanidine which is toxic may also be formed from disintegrating tissues. The absorption of necrotic tissues is ascribable to autolysis or heterolysis. In malignant tumors, much necrosis occurs with subsequent digestion of dead cells so that autolytic products are present in great numbers. Beebe (64) found products of autolysis constantly present in hypernephromas, an angiosarcoma, and a round cell sarcoma. A cancer of the stomach was found to contain autolytic enzymescapable of digesting lung tissue. This toxicity may explain enzymes as a forerunner to metastases. Blumenthal and Wolff (65) believe that tumor tissues have particularly active autolytic enzymes which aid in producing toxic products. It was also shown that tumor ferments exhibited a heterolytic activity which causes infiltrative growth and cachexia,
as Ewing(40) found. Micheli and Donati(66) attribute the hemolytic properties possessed by extracts of malignant tumors to the products of autolysis present. This Petry demonstrated (67) produces hemolysis.

Extracts form malignancies cause hemolysis and are slightly toxic to animals. The cachexia of cancer, states Wells(12), is due to interference to circulation; that areas of necrosis undergoing autolysis to yield toxic and hemolytic substance. That cancer tissues are more permeable to ions than normal tissues, may account for the ready inception of split protein products that aid in the toxicity(68).

Cancer tissue autolyses more rapidly than corresponding normal tissues and its extracts digest other tissues than themselves(heterolysis)(62). Extracts of other tissues fail to do this, tho Muller believes the phenomena due to leucocytes in the blood of tumors. There is an increased antitryptic activity in blood of cancer patients(12). In cachexia, there is an increased elimination of aromatic substances(phenol, indican, oxyacids) that to arise from the abnormal metabolism of tumor proteins. Metabolism in cancer was found to resemble fever, and warrants the assumption that there is 'toxic stimulation to tissue destruction', (12). Vaughan believes that products of protein destruction in cancer are responsible for toxicogenic metabolic abnormality. Malignant tumors show a high proportion of nucleoproteins and products of autolysis are more abundant than in benign tumors. Here there is a great variety of intracellular enzymes(12).

Drew(69) showed that adult cells need degenerating or autolytic processes to proliferate whereas cancer cells are akin to embryonic tissues for they have growth-activating agents—the Tre-
phanes of Carrel-(12). This indicates that toxemias aid in cell proliferation. Gould said(59) that the cancer cell is not an alien cell but it is one influenced by neighboring tissue.

Bendien in his flocculation tests showed a discharging and dehydrating action in tumor tissue. The globulin with a strong negative charge, called cataphoresis, indicates a predisposition to carcinoma. Vaughan(70) notes that a vaccine of dead cancer proteins in a living host brings out characteristic blood changes. It resembles toxic activity. It was prepared from a vaccine that had a toxic and a non-toxic portion. He bases his theory of toxic action on respiratory changes, excitability of the toxic radical, and transitory sensitization using laboratory findings of mononuclear leucocytes. The cancer cell emulsion produced symptoms of dyspnea, chills, fever, low pulse, and finally coma, in rabbits, when it contained the specific ferment. Like most toxic substances, this was soluble. Its peculiarity to malignancies is noted by chemical changes in cells of sarcoma and carcinoma being alike. The sensitizing portion was albuminous in nature though he did not believe the specific enzyme was the same, but rather like Bendien's conclusions, that it of a globulin content. When it a purified state, this simply constructed globulin, he said, was more toxic. In this connexion, Beebe said specific ferments exist in cancer tissue and have a heterolytic activity tho evidence does not prove this beyond doubt(71).

The anoxybiotic cleavage of dextrose is the predominant feature of tumor metabolism described by Warburg(12). Russell, says Eggers(19), found increased amounts of oxidative ferments in rapidly growing malignant tumors, while catalase-defensive enzyme to
toxins were decreased. The oxidative ferments formed the basis of Marshall's (20) contention that cancer tissue combined with ferric oxide to form with leucin, the toxins. He believes the toxins came from metamorphosed epithelial cells.

Metabolism of lipoids is found altered by Pericaud (21) in that lipases are found diminished. The hemolytic poison he describes acts on the lecithins to form toxic lecithin and produces the cachexia. This observation was noted by Loeper, Mechanx, Seze and Far machidis. The metabolism of a cancer cell will induce a lower reduction potential and increased proteolytic activities will make the cell more susceptible to invasion. Altered metabolism is noted by a high glycolysis associated with a defect in respiration which is specific in cancer tissues (72). This is significant in Corkill's experiments on rabbits, for toxemic animals reacted to insulin by a sudden hypoglycemia on injection, with a hyperglycemia later (73).

Metabolism is altered enough to cause abnormal findings in cancer. Enzymes and a specific ferment is in evidence in cancer. The split protein products and unusual number and quality of ferments, show chemical changes occurring in malignant diseases. These have the potentiality of causing toxic symptoms, at the least.
B. EXPERIMENTAL

From experiments on animals and extirpated human tissue, data has been obtained to indicate that toxic products exist in the body due to cancer in some organ. Extracts from carcinomatous tissue was shown to be toxic for protozoa(74). Girard and Mangin claim malignant tumors contain colloidal poisonous substances in proportion to their softness. Extracts from cancer caused paralysis and fall in blood pressure(12). The toxic symptoms displayed resembled cachexia. Seyderhelm and Lampe(12) working on mice, reported that extracts obtained at low temperatures were toxic. The active autolysis at higher temperatures destroyed the cancer poison. Altho this was not confirmed, Mertens(19) also got some toxic material from tumors at low temperatures. Coley made a toxin from an unfiltered mixture of erysipelas and prodigiosus cultures with which he obtained some results in injections for inoperable tumors. Vaughan(70) working on rabbits demonstrated a vaccine of cancer residue having a toxic and non-toxic radical. The latter caused symptoms of poisoning. He based the result on sensitization by a leucocytic rise and fall, and by clinical signs displayed then.

Ross and Cropper(17) in 1908 noted that cancer patients died of symptoms resembling alkaloid poisoning. In experiments, it was noted a phase of excitation occurred in blood of cancer individuals which caused amoeboid movements of the leucocytes. This was attributed to some agent, in small quantities, in the cancer cell. The cancer plasma excited the amoeboid movement which is due also to alkaloids derived from the neighboring tissue. The putrefaction occurring at cancer sites produced ptomaines, and leucomaines which
like choline, cadaverine and putrescine are recognized as toxic alkaloids.

Clinical observation lead Pericaud(21) to the surmise that in cancer, there is a gradual intoxication as the disease progresses. Reiss and Senators support this contention. Oppenheim, observing brains of cancer patients at post-mortem, said there were no lesions in individuals who died after toxic coma. Dyer and Roe(75) in their experiments, noted a decreased glucose tolerance, a mild hyperglycemia, increased glycolytic activity, a slight decrease in Carbon Monoxide combining power and an inconstant variation in pH from sarcomatous implantation, with the hen as a host. This corresponds with findings of hyperglycemia, an increased production of lactic acid from glycogen by cancer tissue over normal(12). Corkill(73) on rabbits, showed that in toxemias, a hyperglycemia was obtained after a sudden fall in the blood sugar level. Increased activity of autolysis was noted in Yoshimoti's experiments(40) on hepatic carcinoma compared to the normal liver and in breast adenocarcinoma versus normal breast tissue. Stoeber and Wilson(19) in 1910, injected split protein products into a rabbit to get malignant skin growths. Ross showed that leucocytes exposed to extracts of dead and decomposing tissues underwent rapid proliferation.
C. IMMUNOLOGICAL AND PATHOLOGICAL

In the study of cancer, certain defensive reactions are noted which are analogous to antigen-antibody and complement fixation phenomena, as seen in bacteriological work. The increased power of cancer serum to inhibit the activity of trypsin and the leucocytic proteases suggests the formation of specific counteractions for the intracellular activity in the disease (12). Animals can be immunized with the formation of various antibodies that Lewin (12) failed to find as specific, yet he accepts this immunity produced by injections of virulent cancer material as an active immunity dependent on cancer antibodies. Pheiffer reported specific anaphylactic antibodies in cancer but his work was unconfirmed. The von Dungern positive complement fixations were based on abnormal products of metabolism liberated in malignancies. Farmachidis claimed that only in malignant disease could the hemolytic activity of cobra venom be inactivated. Korbler (12) found that cancer plasma was more toxic than cancer cells.

Reviewing complement-fixation tests, Hirschberg and Saphir noted that San Pietro and Teso first discovered specific antibodies in cancer serum. Hirzfeld based the results of 300 human sera of internal cancer on specific complement fixing antibodies, that he detected. Using the improved technique, discovered that antibodies existed and believed the reaction is a physico-chemical one due to the action of antigen of carcinoma on serum globulins (77).

Bendien's flocculation reaction indicated that in malignancies, there is inactivated serum. In carcinoma, tuberculosis and pregnancy, the metabolic processes were abnormal. Addition of uric acid or lecithin to cancer serum, increased flocculation while the
fat soluble substances inhibited it. This indicates an increased amount of toxic products are present with the greater flocculation. Antibodies, he concludes, react only when in sufficient amounts in the blood or in the cells. Abderhalden(16) attempted to prove specific ferments existed in carcinoma but Bendien believing they are due to break down end products, acknowledged they did occur in cancer. Where no toxic symptoms were obvious, flocculation started at Tube No. 7, whereas other sera of patients exhibiting toxic signs clinically, began at No 5 or lower. The more malignant the tumor and its toxicity, the earlier did flocculation begin.

Vaughan stated that the body cells normally have an anti-ferment often absent in cancer, to explain the inability to destroy cancer cells. Immunity was based on these antiferments. Marshall (20) stated that the serum of carcinoma undergoing flocculation is due to hemolysis of leucocytes by the action of ferric oxide and the leucothaemates. He said the defensive reaction of tissues depended on formation of oxidases and leucocytes that neutralize the toxins. Pericaud links anaphylaxis with immunity, in that it is a defense reaction of the cells against the toxin. Saying that certain toxins in small doses are used to preserve the cells of an organ against the more deadly toxins, he lays the foundation for treatment. This process may be the one utilized by Coley in injection of bacterial cultures for cancer relief. This process of immunization for non-specific toxins was called 'phylaxis' by Billard(21).

Non-Specific cytotoxins, heterotoxins, were demonstrated in the fresh serum of normal animals as being effective against tumor cells and cells of foreign elements. The cytotoxins were described as labile immune bodies ineffective without complement. Lumsden and Kohn-
Speyer (78) believe certain elements are extravasated from leucocytes which aid the antibodies. Specie differentiation in antibody defense was noted in the existence of a labile cytotoxin having a special affinity for cancer cells. This was called the eu-globulin fraction of anticancer serum. It is concluded that antibodies exist that have a special affinity for cancer cells (79).

Kast and Killian (80) state that large proportions of the cases exhibit renal injury either from products of the tumor or from a bacterial infection. The ability of cancer cells to attack adjacent tissues without phagocytic processes indicate that some tissue solvent substance is produced. The readiness in which they attack bone supports the view. In diffuse cancer of the serous membranes, the severe hemorrhagic exudation commonly seen suggests the presence of a toxic agent which Grawitz (81) points out, resembles tuberculin in its effects. Bard showed these exudates are more rapidly hemolyzed as compared to exudation from other sources.

Glycogen is readily changed to lactic acid which softens the surrounding area for invasion by carcinomatous cells (12). That the alkalinity of the blood is related to malignancy, is indicated by many observers but the irregularity of cells in cancer tissue is increased in patients with an alkaline pH of blood (82). It is likely that other pathological findings in the excretory organs like the liver and kidney would be seen in cancer patients to denote toxic effect had occurred, if examination were made at autopsy and surgical extirpation.
D. SEROLOGICAL AND DIAGNOSTIC

Probably the most significant change is the occurrence of hyperglycemia and altered sugar tolerance. Williams and Humphrey point out (84) there is dietary increase in the blood sugar in cancer, the level rising higher and enduring longer than normal. This is confirmed by Kast and Killian in 1921, and Hoffo and Rivarola in 1924. Rohdenburg, Bernhard and Kruehbiel (85) showed the sugar tolerance curve was typically different from the normal and other diseases, as shown below:

![Graph showing sugar tolerance curves]

Beregoff (86) found the same positive carbohydrate curve and the low glucose tolerance. Friedenwald and Grove (87) recognized the typical glycemia curve and blood sugar tolerance test and compared this curve to other conditions:

![Graph comparing sugar tolerance curves]

Kelly found the hyperglycemia occurring in all cancers, particularly in the gastro-intestinal tract. Untreated cases of cancer had hyperglycemia easily demonstrated by Behan and Shaw. Later Woodward and Fry and other observers (88) showed this was a definite entity. Some believed this a manifestation of toxicity in cancer.
The relationship of increased cholesterol in the blood has been claimed to be the cause of increased cellular proliferation. That it is increased in cancer serum and plasma is proven by De Niord\(^{12}\) and by Robertson and Burnett\(^{12}\). Later Matteck and Buchwald\(^{89}\) found cholesterol much higher in plasma of cancer patients than in normal while the latter's whole blood serum-cholesterol ranged higher than cancer individuals. This was confirmed in later publications in cancer research. Currie in England, confirmed a hypercholesterolemia in cancer. Luden\(^{90}\) in X-ray studies found an increased cholesterol in blood due to a disturbance in its metabolism. Willheims and Fuchs pointed out that the connective tissue stroma of carcinoma had a high cholesterol content. Bullock and Cramer showed the lecithin-cholesterol ratio higher in rapidly growing tumors, and Jowett demonstrated that pure malignant tissues have a higher phosphatide and cholesterol content with a higher ratio between the two. The cholesterol in plasma had a higher proportion than normal.

The finding of an altered globulin-albumin ratio with the former increased in amount is associated with the cancer cachexia as Galehr \(^{12}\) pointed out. This was confirmed by Gussio \(^{91}\) who showed the albumin abnormally low. He too says it accompanies the debility and occurs quite early in cancer. This formed the basis of the Bothelho and Kahn's Albumin A reactions. To some extent, the reactions of Wigand, Bendien, Coke, Schmitz-Wulkow's Neutral Red of Raffo, and Douris and Giquel are based on the Albumin-Globulin ratio. Boyland showed serum globulin was increased in cancer. Kennaway found increased globulin coming from the tumor and decreased albumin.

Serum colloids \(^{12}\) showed a greater degree of dispersion in cancer serum over normal human serum and blood from a cancerous
tissue had a greater dispersion than that from other organs of the same body. Waterman showed that cancer cells have highly dispersed surface colloids. This is inversely related to calcium ions in the serum. Colloid Nitrogen precipitated from urine of cancer patients is increased over normal amounts and Salkowski shows it to be higher in cancer than other pathological conditions. The Meiostagamin reaction is based on this colloid phenomenon. The Salomon-Saxl reaction is a test for colloidal and neutral sulphur in the urine. The colloid Nitrogen is increased in cancer cases over total nitrogen. This colloid Nitrogen may be toxic when in unusual amounts.

Wells (12) found that cancer sera NPN and urea-N are found lower than the normal figures while urea and uric acid were slightly higher. Theis and Stone confirmed this. Carbonuria was found to be predominant over nitrogen in the urine by Medvedka. Kluyver (23) found that in cancer the protein sols were in a chronic stage of peptization. The interferometer method of diagnosis is based on the specific proteolysis of substrate—a digestive breakdown. The Fuchs test, using fibrin, is based on proteolysis, as is the Abderhalden and the colloid-flocculation reaction of Fry. The Thomas Binetti reactions were found due to bacterial products causing the digestion and consequent discoloration of dye. It is evidence that toxic reaction lies behind some of the changes manifest by the diagnostic procedures.

Jacques Loeb (92) discovered that "individual serum salts by themselves and acting singly are cell poisons, though in proper proportions, these salts have a natural detoxifying action on each other." Many observers noted changes in Calcium, Magnesium, Potassium and Phosphorus relations in Cancer. There is an excessive elimination of mineral salts. Ewing(40) notes
that demineralization occurs in cancer cachexia along with Nitrogen loss. Donnan indicates a decrease in Calcium ions with the increased dispersion of sols. Wells (12) believes hypocalcemia occurs with a hyperkalemia. This is confirmed by Jackson and Taylor, who associate this with the alkalosis of the blood serum; by Shear, who noted no significant changes in Sodium or Magnesium; by Soehla, who paralleled the reduced calcium with the decrease of the surface tension of the blood serum; by Paolucci, who found a distinct hypocalcemia with metastasis; by Theis and Benedict, although their figures for Potassium were close to normal; by Clowes and Frisbee (5); and by Beregoff (86).

Potassium in serum of cancer patients was small, but increased in the blood plasma. Hyperkalemia was found in corpuscles by Cantegril. Calcium in mice cancers was found to be lower than normal by Parfentjev. The hyperkalemia was noted by Pitts and Johnson (93), and by Clowes and Beebe (40) in rapidly growing tumors. Regarding Phosphorus, Byron and Kay found an increased phosphorus in patients who had cancer with anemia. Youngburg and others found increased phosphorus values even without regard to anemia. Likewise Phosphatide values were higher than normal.

The sensitization reactions by the intracutaneous injection technique offered by Mertens (40), Grushkin (94), Boyksen (40), Wigand and others are based on foreign protein of embryonal character producing specific precipitins and allergic reaction. The complement-fixation tests and the labile reactions are based on immunity and the theory that of the antilytic agents, which normally exist are not present or fail to develop, malignancy is permitted to grow. Von Dungern made the complement deviatory power of cancer serum the basis of his diagnostic procedures.
Brieger and Tiebing in 1908, followed by Weil, showed that the antitryptic index denotes the power of blood serum to inhibit the digestive action of trypsin. Eggers (19) notes that this may point to the cachexia.

Most observers agree on the alkalinity of blood serum in cancer despite observations that there are intracellular acid reactions and that cancer develops in areas having an acid secretion, or are prone to acid fermentation (45). This alkalascence is noted by Moore and Wilson (12), Rohdenburg (19), Ely, Beregooff (86), Ewing (38), Woodward and Fry (88), Schoonover, Meyer (31), Pitts and Johnson (93), Reding and Menten and others. The whole blood test of Brossa was based on the premise that cancer blood had certain agents within to cause changes in dyes, and a later erythrocytic fall.

The sedimentation test is a simple one, which in the absence of other toxic conditions, may indicate presence of cancer if the time of sedimentation is high. Wells (12) found this true and based it on high globulin and fibrinogen content. Kecheis noted increased rate in carcinoma of female genital tract (96). Gragert (97) noted the accelerated rate as being "the prognostic sign in the relief of toxic activities," and the "rate of acceleration of sedimentation is not proportional to the size of cancer but reflects the toxic action on the system." Rubin (27) called the increase due to a physico-chemical phenomenon. Many other observers confirmed the increased rate of sedimentation in cancer. Remond, Ravinia and Zigina (98) used a cytolytic reaction test for diagnosis on the basis that cancer cells have a strong cytolytic power over gastric mucosa, particularly if it is an alimentary cancer.
Narat (54) calls the above diagnostic and serological findings as kataplasia-traceable to morphological, physical and chemical changes found in cancer cells and serum of patients afflicted with the malignant tumor. These changes may be readily conceived as toxic manifestations. He sums them as increased: permeability of tumor cells, coagulability of blood, BMR, fibrinogen, nucleoproteids, globulins, potassium, phosphorus, phosphatids, fermentative glycolysis, cholesterolemia, and a higher proteolytic titre. Decreased are the albumins, surface tension of serum, tryptophan, calcium, and viscosity of serum. Alkalosis of blood is noted.
TREATMENT

In the main, therapy should be directed toward cure or relief. Cancer is a systemic disease (99). Treatment should be aimed at the findings discussed above. It is a disease having a local origin and systemic effects. Cure is obtainable by removing the cancer tissue early and thereby eliminating the sources of toxemias. The latter should be kept in mind for death results from toxic elements and rarely from the overgrowth of tissue per se. Symptomatic relief is possible, for toxemias are likely to be present.

Exirpation of the local growth will eliminate the source of the toxins. X-ray and radium are best suited for external growths and for these cells infiltrating surrounding tissues. Luden (90) points out that radiological therapy increases cellular resistance. Alkalosis, whether it is the fore­runner of cancer, definitely exists. Willy Meyer (99) advises treatment against this general condition by inducing acidosis in the blood stream. He suggests fever producing agents, Coley's fluid, starvation, artificial hyperemia, induced inflammation, administration of paraphyroid extract of calcium, of acids, and breathing pure oxygen admixt with 4½ per cent carbon dioxide and, lastly, X-ray. To counteract this alkalin­ity, Pericaud (21) suggests giving pure cholesterin with sub­stances having the hydroxyl radical. Radium and X-ray produce a local acidity that aids the general alkalascence.

Coley's toxin (43), not only aids the alkalinity of the medium, but results in local inflammatory reaction with increased irritation. The Coffey-Humber serum (100) a suprarenal cortex extract, given to patients aided the general condition for
they were relieved of psychic depression, felt better and
gained weight, even when inoperable. It was given on the
premise that the patient lacked a certain vital principle.
In three cases in France, of inoperable cancer, protein
therapy by subcutaneous reinjection of the patient's own
serum gave a subsidence of pain, decrease in tumor size, and
subjective relief. Vaccines have been made from the tumor
extract with questionable results. Gianturo (101) using the
Freund and Kaminer principle, that normal cells can hemolyze
cancer cells, injected normal blood serum directly into cancer-
ous growths or intravenously into individuals afflicted with
cancer. Others failed to obtain similar good results.

With evidence of a deficiency in minerals, observers
administered calcium ions which Monceaux (16) noted had a good
effect on cancer. Likewise, Wolf, Watermann, Sauerbrach, et al
(16) say that Magnesium had a good effect on carcinoma. This is
furthered by observers who noted an avitaminoses in people with
cancer and suggest administration of vitamin containing food.

Endocrine therapy is advanced by Ishehara (103), who like
Grushkin's diagnostic procedures, bases his therapeutic measure
on embryonic substances. He made a P-0-U-hormone for cancer of
cervix with erosion and made it obtainable in tablet form.
Marshall (20) intimates that endocrine glands—pituitary, para-
thyroid and suprarenal—are responsible for the presence of
sarcomatous and carcinomatous toxins.

Beebe compiled a complicated pharmacological formula of
vegetable drugs which bring definite relief to cancer patients(104).
Many men have made bacterial vaccines with some effect. Blair Bell
used colloidal lead, because lecithin-rich tissues have an affinity for lead. Guyer and Mohs (105) used colloidal platinum which inhibited cancer by augmenting the body's defenses against cancer in the production of inflammation and fibrosis.

In general, the best theraeusis is to build up the general health, treat anemia, promote acidosis, use of high vitamin diet, increase certain minerals and obtain surgical extirpation and radiological infiltration. It is best to promote inflammation, wall off by fibrosis, destroy, wherever possible, the secondary invading bacteria, and eliminate bacteria foci of infection. Burrows (102) in the London Cancer Hospital tried to find a specific remedy for the Jensen Rat Sarcoma by using acids, calcium chloride, minced liver, saponin, thorium, gelatine, alum, and the ligations of various blood supply; but concluded, none were specific. Yet, he found a higher per-cent of retrogressions occurred in the treated animals than among the untreated. This is evidence enough that therapy should always be tried, whether for cure or for symptomatic relief.
CONCLUSION

The author has attempted to present such evidence that may prove that toxemias exist in malignant conditions, by giving the nature, the sources, the clinical and laboratory symptoms, signs and findings; and in brief form, a resume of general management of toxemias as determined by the observations of many authors. It does not purport to be a complete exploitation of the subject, but to his knowledge, the first time that the subject of toxemias of cancer has ever been presented per se. He has not attempted to prove that it exists by actual isolation, but has shown that it exists from laboratory data and clinical experience, no matter what the source. If the reader becomes aware of a picture of cancer as a generalized whole rather than a mere local disease and remembers it as such when therapeutic measures must be considered, the author will consider his efforts more than repaid.
CASE I CA of Stomach (51)
Illustrating Fever Signs in Cancer

A laborer, 59 years old, entered the hospital April 19, with the complaints of malaise, weakness, and loss of 25 lbs in past four months with constant abdominal pain, of indefinite character. The examination showed a pale man weighing 137 pounds. Head, neck, lungs were negative, slight murmur with cardiac enlargement, small bulge in midepigastrium, liver enlarged. There was a achlorhydria, occult blood in stool, anemia marked, leucos negative, and a month later, the barium meal showed a six hour residue. Operation May 20, revealed diffuse infiltrative carcinomatosis. Nothing done, and patient died July 21st. During first 18 days, fever was irregular, diurnal variation of 1-5 degrees, from 97 to 103.4 and an average of 101. Nothing was found clinically other than the stomach growth to account for fever. Three weeks later, temperature subsided with but two isolated rises, followed by a gradual rising pyrexia. Post-Mortem examination disclosed no other existent cause for fever but the tumor tissue.

CASE II CA of BREAST (63)
Illustrating Anemia of Cancer

A woman of 54 noticed a lump in breast and complained of lameness in hip and back getting worse. She was a very pale, obese woman with a mass involving nipple and upper outer quadrant of the right side with ulcerated masses in axilla and two enlarged lymph nodes. Metastatic malignancy evident from X-ray of pelvis, hip, spine, clavicle, ribs, femur. Blood showed 10,700 whites, 1,350,000 reds and 32% Sahli hemoglobin with 53% polys and 43% lymphos. Achromia and anisocytosis marked. The high color index (1.2) differs from P.A. and from usual secondary of cancer. It is explained by the metastatic bone involvement. This too indicates toxic action on cells
CASE III CA of Rectum (108)
Illustrating Loss of Weight

A man aged 51, after having seen four physicians came to the hospital complaining of obstipation, dysuria, abdominal pain rectal pain for past five months, Diagnosis on examination was carcinoma of the recto-sigmoid junction. A colostomy was performed. The chief complaint was anorexia, indigestion, mucopurulent rectal discharge and nocturia. The outstanding point was the loss of 50 pounds in six months. Prognosis was poor. General advanced symptoms of cancer probably follow later.

CASE IV CARCINOMATOSIS (106)
Illustrating Effects of Cancer felt before Demonstrable Evidence of the Tumor Mass is Diagnosed.

A veteran of the war, aged 39, complained of stomach trouble. He had four attacks of upper right quadrant abdominal pain radiating to epigastrium, and sensations of distension and fullness. Loss of weight was negligible. Pleurisy with effusion was diagnosed and much fluid was drained off over several months until artificial pneumothorax was established. Xray of G.I. was negative except for the irregularity of outline of the lesser curvature of the stomach. Several months later, the anterior cervical and axillary lymph nodes enlarged. The pathological report was adenocarcinoma of the bronchial mucosa or intestinal tract. The diagnosis was one of Diffuse Carcinomatosis.

Case V Diagnosis of Carcinoma (16)
Illustrating that Diagnosis of Cancer may be made thru the Specific Changes in the Blood Serum.

In a series of over 1500 studies of sera, Bendien reached the conclusion that in carcinoma where toxic symptoms were present,
flocculation in the 20 test tubes began at number 5 or below while in cancer without toxicity displayed, it began at 6. The normals were in 480 cases at 6. The normal serum at 65 years of age or above were at 7 or 8. Active tuberculosis flocculated at 1 to 5 in 164 cases. Carcinoma in 238 cases were at 1-5. Gall Bladder with Jaundice in 21 cases also started at 1-5 while that without icterus began at 5 in six cases. Pleurisy in 10 cases, malaria in five, and nephritis in 34 began from 3-5. Spectroscopic examination eliminates tbc and jaundice the gall bladder condition, to make a positive diagnosis of cancer by serological study, particularly in cases of toxicity manifested.

CASE VI Cancer Therapy Via Acidosis (107)
Illustrating treatment of the general condition

Mrs. T in Spring 1928 became weak, pale, had heart burn, and lost weight rapidly. Xray diagnosis was gastric ulcer. In July there was an achlorhydria, anorexia, and stomach cramps. The next month at Battle Creek, with occult blood in stools an Xray diagnosis was made of Inoperable Cancer of the Stomach. Operation was performed Oct 31, 1928 at the Mayo Clinic after she lost over 25 lbs and operation revealed inoperable leather neck type of tumor with glandular enlargement tho there was no obstruction. Clinical and pathological evidence pointed to carcinoma. Hearing of Prof Fischer-Wasels acidosis therapy in Frankfurt, Germany, she appeared there on Dec 9 in a bad condition. Cachexia, cramps, poor food ingestion, pains she weighed 133 lbs. The tumor mass was size of child's head. She was given HCl acid 10-35 gtts increasingly tid, deep Xray 15 minutes ea week and C62-02 gas bid in three stages of 40 minutes. On May 1st, no tumor was palpable nor could Xray demonstrate it. Pt felt fine. Discharged two weeks later and received like treatment—prophylactic—
two different times after that. When Dr. Meyer examined her, he found a 56 year old woman, in October 1931, who had negative chest findings, no vaginal infiltration, good appetite, using a mineral oil for bowel movements and weighed 172 pounds stripped. The pH was 7.338 (normal), red blood count of 3,610,000, hemoglobin of 73% and a white count of 6,500. The conclusion is that there is sufficient evidence that an unmistakable gastric cancer was receded both in general and local ways by the acidosis therapy of building up the body.
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